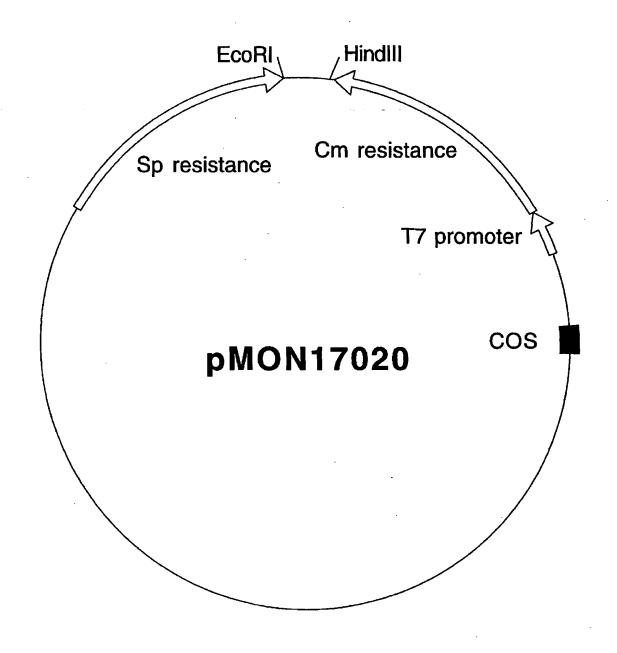
6477 6597 6657 TGAAATAAGTTTAACCATAGCGGTTTTTGGTTCTTCCTTGAGGGTAGGAGTTTCCAAACAT **AGGAAGAATTCTCAGTCCAAAGCCTCAACAAGGTCAGGGTACAGAGTCTCCAAACCATTA** ACTTTATTCAAATTGGTATCGCCAAAACCAAGAAGGAACTCCCATCCTCAAAGGTTTGTA TCCTTCTTAAGAGTCAGGTTTCGGAGTTGTTCCAGTCCCATGTCTCAGAGGTTTGGTAAT CGGTTTTCGATGTCCTCTAGTTACTTTAGAAGTTAGTTTCATTTGATGACAAGGTCGT CATGCATCATGGTCAGTAAGTTTCAGAAAAAGACATCCACCGAAGACTTAAAGTTAGTGG GTACGTAGTACCAGTCATTCAAAGTCTTTTTCTGTAGGTGGCTTCTGAATTTCAATCACC SspI 6538

| 1 | 5898 |
|------------|---|
| 6954 | SSDI |
| Fu | 6838 TGTCGGGTGAGTGATTACGCATACTGCTTGCGTCACTGCTGGTGTTTTTTTT |
| 4 6897 | ACAGCCCACTCACTAATGCGTATGACGAACGCAGTGACGACCACAAAAAAATTCCCTCTA |
| () | 6778 TATTTCGTCTAAGGAGATCATGTTCACCCCTTGTTTTATTGCACCTTTTCGCACGGACAGGAC |
| 5 6837 | ATAAAGCAGATTCCTCTAGTACAAGTGGGGAACAAATAACGTGGAAAAAGAGCTGTCCTG |
| <i>(</i>) | 6718 TCCTTACCACGTCTTAACAATCCGCGTGGATGGTTTTCGTAGAAACGGAAATAACGTTTTC |
| 6777 | AGGAATGGTGCAGAATTGTTAGGCGCACCTACCAAAAGCATCTTTGCCTTTATTGCCAAAG |
| | 6658 CGTAGAAACTTTCATTAGAACAGTTGTAGCTCGTCGACCGAACACCCCTGGTCTGTTTTT |
| 4 6717 | GCATCTTTGAAAGTAATCTTGTCAACATCGAGCAGCTGGCTTGTGGGGACCAGACAAAA |



Figure

| | U.S | . P | ato | ent | |
|--|-----|-----|-----|-----|--|
|--|-----|-----|-----|-----|--|

| Mav | 27. | 1997 |
|-------|------------|------|
| TATUL | <i>4</i> , | エノノリ |

| Sheet | 4 | οf | 70 |
|-------|---|-----|-----|
| OHEEL | 4 | CH. | /1/ |

| 5,633 | 435 |
|-------|-----|
| -,; | , |

| 4 | |
|--------|---|
| 1 2 | ł |
| בב | Ŋ |
| Ī | į |

·

| Patent | May 27, 1997 | Sheet 4 of 70 | 5,633,435 | |
|---|--|---|--|--|
| 106 | 154 | 250 | 346 | |
| AAGCCCGCGT TCTCTCCGGC GCTCCGCCCG GAGAGCCGTG GATAGATTAA GGAAGACGCC C ATG TCG CAC GGT GCA AGC AGC CGG CCC GCA ACC GCC CGC AAA TCC Met Ser His Gly Ala Ser Ser Arg Pro Ala Thr Ala Arg Lys Ser 1 5 15 | TCT GGC CTT TCC GGA ACC GTC CGC ATT CCC GGC GAC AAG TCG ATC TCC Ser Gly Leu Ser Gly Thr Val Arg Ile Pro Gly Asp Lys Ser Ile Ser 20 30 30 ACC CGG TCC TTC ATG TTC GGC GGT CTC GCG AGC GGT GAA ACG CGC ATC His Arg Ser Phe Met Phe Gly Gly Leu Ala Ser Gly Glu Thr Arg Ile 40 40 415 | GAA GGC GAG GAC GGlu Gly Glu Asp V55 GCC AGG ATC CGT AAIA Arg IA | GAT GGC GTC GGC AAT GGC GGC CTC CTG GCG CCT GAG GCG CCG CTC GAT Asp Gly Val Gly Asn Gly Gly Leu Leu Ala Pro Glu Ala Pro Leu Asp 90 85 85 85 85 85 95 | |

| Ü | J.S. Pate | ent | May 27, | 1997 | Sheet 5 o | f 70 | 5,63 | 33,435 |
|---|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|---------------------|--------|
| | | | , | | | • | - , | , |
| | | | | | | | | |
| | 394 | 442 | 490 | 538 | 586 | 634 | 682 | |
| | ĸ | 4 | 4 | ഗ | ហ | . | 9 | |
| | GGG Gly | AAG Lys | CAG Gln | CCG | CAG Gln 175 | ACG Thr | CTG Leu | |
| | GTC (Val (| ACA A | GTG (Val (| 666 (| GCA CAIA CAIA CAIA | ATC # Ile 1 | ATG C Met I | |
| | CTC | CTC Leu 125 | GGC Gly | CGC (Arg (| TCC (Ser | 66C . | AAG Lys 1 205 | 3B |
| | GGC Gly | TCG Ser | ATG Met 140 | TTG Leu | GCC Ala | CCC | GAA Glu | a) |
| | ATG Met | GCC Ala | GAA Glu | ACC Thr 155 | ATG Met | ACG Thr | ACG Thr | Figur |
| | ACC Thr | GAC Asp | CGC Arg | GTT Val | CCG Pro 170 | AAC Asn | CAT His | |
| | CTG Leu 105 | GGC Gly | CTG | CCC | GTG Val | CTC Leu 185 | GAT Asp | щ |
| | CGC Arg | ATC Ile 120 | CCG | CTT Leu | CGC Arg | GGC Gly | CGC Arg 200 | |
| | TGC Cys | TTC | AAC Asn 135 | CGT Arg | TAC | GCC Ala | ACG Thr | |
| | GGC G1y | ACC Thr | TTG Leu | GAC ASD 150 | ACC Thr | CTC | ATG Met | |
| | ACG Thr | AGC Ser | GTG Val | GGT Gly | ATC Ile 165 | CTG Leu | ATC Ile | |
| | GCC Ala 100 | GAC Asp | CGC Arg | GAC Asp | CCG | GTG Val 180 | CCG | |
| | GCC Ala | TTC Phe 115 | GGC GlY | GAA Glu | ACG Thr | GCC Ala | GAG Glu 195 | |
| | AAT Asn | GAT Asp | ATG Met 130 | TCG | CCG Pro | TCC Ser | ATC Ile | |
| | 66C 61y | TAC Tyr | CCG Pro | AAA Lys 145 | ACG Thr | AAG Lys | GTC Val | |
| | TTC | GTC Val | CGC Arg | GTG Val | AAG Lys 160 | GTG Val | ACG Thr | |
| | | | | | | | | |

| U.S. Patent | May 27, | 1997 | Sheet 6 | of 70 | 5,63 | 33,435 |
|--|---|---|---|---|---|-----------|
| | | | | · | | |
| 730 | 826 | 874 | 922 | 970 | 1018 | |
| C TTT GGC GCC AAC CTT ACC GTC GAG ACG GAT GCG GAC GGC GTG Y Phe Gly Ala Asn Leu Thr Val Glu Thr Asp Ala Asp Gly Val 210 C ATC CGC CTG GAA GGC CGC GGC AAG CTC ACC GGC CAA GTC ATC T Ile Arg Leu Glu Gly Arg Gly Lys Leu Thr Gly Gln Val Ile 5 | G CCG GGC GAC CCG TCC TCG ACG GCC TTC CCG CTG GTT GCG GCC 1 Pro Gly Asp Pro Ser Ser Thr Ala Phe Pro Leu Val Ala Ala 245 | T GTT CCG GGC TCC GAC GTC ACC ATC CTC AAC GTG CTG ATG AAC u Val Pro Gly Ser Asp Val Thr Ile Leu Asn Val Leu Met Asn 260 | C CGC ACC GGC CTC ATC CTG ACG CTG CAG GAA ATG GGC GCC GAC r Arg Thr Gly Leu Ile Leu Thr Leu Gln Glu Met Gly Ala Asp 275 | A GTC ATC AAC CCG CGC CTT GCC GGC GGC GAA GAC GTG GCG GAC u Val Ile Asn Pro Arg Leu Ala Gly Gly Glu Asp Val Ala Asp 290 | C GTT CGC TCC TCC ACG CTG AAG GGC GTC ACG GTG CCG GAA GAC g Val Arg Ser Ser Thr Leu Lys Gly Val Thr Val Pro Glu Asp 5 | Figure 3C |
| CAG GGC Gln Gly CGC ACC Arg Thr | GAC GTG ASP Val 240 | CTG CTT Leu Leu | CCC ACC Pro Thr | ATC GAA Ile Glu | CTG CGC Leù Arg 305 | |

| U.S. I | Patent |
|--------|--------|
|--------|--------|

| May | 27. | 1997 |
|-------|-----|------|
| IVIAV | 41, | 1771 |

| Sheet | 7 | of | 70 |
|-------|---|----|-----------|
|-------|---|----|-----------|

| 5,633 | 3,435 |
|-------|-------|
| -, | , |

| 3D |
|------------|
| a |
| re |
| gu |
| - H |
| Ŀ |

| 1066 | 1114 | 1162 | 1210 | 1258 | 1306 | 1354 |
|---|---|---|--|---|--|---|
| GCG CCT TCG ATG ATC GAC GAA TAT CCG ATT CTC GCT GTC GCC GCC 106 Ala Ala Ala Ala Ala Ala 325 | TTC GCG GAA GGG GCG ACC GTG ATG AAC GGT CTG GAA GAA CTC CGC 111 Phe Ala Glu Gly Ala Thr Val Met Asn Gly Leu Glu Glu Leu Arg 340 | AAG GAA AGC GAC CGC CTC TCG GCC GTC GCC AAT GGC CTC AAG CTC Lys Glu Ser Asp Arg Leu Ser Ala Val Ala Asn Gly Leu Lys Leu 355 | GTG GAT TGC GAT GAG GGC GAG ACG TCG CTC GTC GTG CGC GGC 12 Val Asp Cys Asp Glu Gly Glu Thr Ser Leu Val Val Arg Gly 370 | GAC GGC AAG GGG CTC GGC AAC GCC TCG GGC GCC GCC GTC GCC ASp Gly Lys Gly Leu Gly Asn Ala Ser Gly Ala Ala Val Ala 390 | CTC GAT CAC CGC ATC GCC ATG AGC TTC CTC GTC ATG GGC CTC 13 Leu Asp His Arg Ile Ala Met Ser Phe Leu Val Met Gly Leu 415 | GAA AAC CCT GTC ACG GTG GAC GAT GCC ACG ATG ATC GCC ACG Glu Asn Pro Val Thr Val Asp Asp Ala Thr Met Ile Ala Thr 420 |
| CGC GC Arg Ai | GCC T7 Ala PP | GTC AA Val Ly | AAT GGC Asn Gly | CGC CCT Arg Pro 385 | ACC CAT Thr His | GTG TCG Val Ser |

| AGC TTC CCG GAG TTC ATG GAC CTG ATG GCC GGG CTG GGC GCG AAG ATC Ser Phe Pro Glu Phe Met Asp Leu Met Ala Gly Leu Gly Ala Lys Ile 445 | U.S. Pate |
|---|--------------------|
| GAA CTC TCC GAT ACG AAG GCT GCC TGATGACCTT CACAATCGCC ATCGATGGTC Glu Leu Ser Asp Thr Lys Ala Ala 450 | 1456 t |
| CGGCAAGGGG A | 1516 |
| ATCTCGATAC GGGCCTGACC TATCGCGCCA CGGCCAAAGC GCTGCTCGAT CGCGGCCTGT | 27, 19 |
| CGCTTGATGA CGAGGCGGTT GCGGCCGATG TCGCCCGCAA TCTCGATCTT GCCGGGCTCG | 97 |
| ACCGGTCGGT GCTGTCGGCC CATGCCATCG GCGAGGCGGC TTCGAAGATC GCGGTCATGC | 1696 S |
| CCTCGGTGCG GCGGGCGCTG GTCGAGGCGC AGCGCAGCTT TGCGGCGCGCGT GAGCCGGGCA | 1756 Peet 8 |
| CGGTGCTGGA TGGACGCGAT ATCGGCACGG TGGTCTGCCC GGATGCGCCG GTGAAGCTCT | 1816 |
| ATGTCACCGC GTCACCGGAA GTGCGCGCGA AACGCCGCTA TGACGAAATC CTCGGCAATG | 1876 |
| GCGGGTTGGC CGATTACGGG ACGATCCTCG AGGATATCCG CCGCCGCGAC GAGCGGGACA | 1936 |
| TGGGTCGGGC GGACAGTCCT TTGAAGCCCG CCGACGATGC GCACTT | 5,63 |
| Figure 3E | 33,435 |

| U.S. I | Patent | May : | 27, 1997 | Sheet 9 | of 70 | 5,6 | 33,435 |
|---|---|--|--|--|--|--|-----------|
| 09 | 112 | 160 | 208 | 256 | 304 | 352 | |
| GTAGCCACAC ATAATTACTA TAGCTAGGAA GCCCGCTATC TCTCAATCCC GCGTGATCGC | GCCAAAATGT GACTGTGAAA AATCC ATG TCC CAT TCT GCA TCC CCG AAA CCA Met Ser His Ser Ala Ser Pro Lys Pro 1 | GCA ACC GCC CGC TCG GAG GCA CTC ACG GGC GAA ÁTC CGC ATT CCG Ala Thr Ala Arg Arg Ser Glu Ala Leu Thr Gly Glu Ile Arg Ile Pro 10 | GGC GAC AAG TCC ATC TCG CAT CGC TCC TTC ATG TTT GGC GGT CTC GCA Gly Asp Lys Ser Ile Ser His Arg Ser Phe Met Phe Gly Gly Leu Ala 30 | TCG GGC GAA ACC CGC ATC ACC GGC CTT CTG GAA GGC GAG GAC GTC ATC Ser Gly Glu Thr Arg Ile Thr Gly Leu Leu Glu Gly Glu Asp Val Ile 50 | AAT ACA GGC CGC GCC ATG CAG GCC ATG GGC GCG AAA ATC CGT AAA GAG Asn Thr Gly Arg Ala Met Gln Ala Met Gly Ala Lys Ile Arg Lys Glu 60 | GGC GAT GTC TGG ATC ATC AAC GGC GTC GGC AAT GGC TGC CTG TTG CAG Gly Asp Val Trp Ile Ile Asn Gly Val Gly Asn Gly Cys Leu Leu Gln 75 | Figure 4A |

| U.S. Pate | ent | May 27, | 1997 | Sheet 10 | of 70 | 5,63 | 33,435 |
|--|---|---|---|---|---|---|-----------|
| 400 | 448 | 496 | 544 | 592 | 640 | . 889 | |
| CCC GAA GCT GCG CTC GAT TTC GGC AAT GCC GGA ACC GGC GCG CGC CTC Pro Glu Ala Ala Leu Asp Phe Gly Asn Ala Gly Thr Gly Ala Arg Leu 90 | ACC ATG GGC CTT GTC GGC ACC TAT GAC ATG AAG ACC TCC TTT ATC GGC Thr Met Gly Leu Val Gly Thr Tyr Asp Met Lys Thr Ser Phe Ile Gly 110 | GAC GCC TCG CTG TCG AAG CGC CCG ATG GGC CGC GTG CTG AAC CCG TTG Asp Ala Ser Leu Ser Lys Arg Pro Met Gly Arg Val Leu Asn Pro Leu 135 | CGC GAA ATG GGC GTT CAG GTG GAA GCA GCC GAT GGC GAC CGC ATG CCG Arg Glu Met Gly Val Gln Val Glu Ala Ala Asp Gly Asp Arg Met Pro 140 | CTG ACG CTG ATC GGC CCG AAG ACG GCC AAT CCG ATC ACC TAT CGC GTG Leu Thr Leu Ile Gly Pro Lys Thr Ala Asn Pro Ile Thr Tyr Arg Val 155 | CCG ATG GCC TCC GCG CAG GTA AAA TCC GCC GTG CTG CTC GCC GGT CTC Pro Met Ala Ser Ala Gln Val Lys Ser Ala Val Leu Leu Ala Gly Leu 170 | AAC ACG CCG GGC GTC ACC GTC ATC GAG CCG GTC ATG ACC CGC GAC Asn Thr Pro Gly Val Thr Thr Val Ile Glu Pro Val Met Thr Arg Asp 190 | Figure 4B |

| U.S. Pate | ent | May 27, | 1997 | Sheet 11 | of 70 | 5,6. | 33,435 |
|---|---|---|---|---|---|---|-----------|
| 736 | 784 | 832 | 880 | 928 | 976 | 1024 | |
| CAG GGC TTT GGC GCC GAC CTC ACG GTC GAG Gln Gly Phe Gly Ala Asp Leu Thr Val Glu 210 | CGC CAT ATC CGC ATC ACC GGC CAG GGC AAG Arg His Ile Arg Ile Thr Gly Gln Gly Lys 225 | GAC GTG CCG GGC GAT CCG TCA TCG ACC GCC Asp Val Pro Gly Asp Pro Ser Ser Thr Ala 240 | CTT CTG GTG GAA GGT TCC GAC GTC ACC ATC Leu Leu Val Glu Gly Ser Asp Val Thr Ile 265 | CCG ACC CGT ACC GGC CTC ATC CTC ACC TTG Pro Thr Arg Thr Gly Leu Ile Leu Thr Leu 275 | ATC GAA GTG CTC AAT GCC CGT CTT GCA GGC Ile Glu Val Leu Asn Ala Arg Leu Ala Gly 295 | CTG CGC GTC AGG GCT TCG AAG CTC AAG GGC Leu Arg Val Arg Ala Ser Lys Leu Lys Gly 305 | Figure 4C |

AAC (

CTG ATG 7 Leu Met 7

CGC AAC GTG (Arg Asn Val I

GCC Ala 255

CCG CTC GTT GCC Pro Leu Val Ala

TTC Phe 250

GCC GAT A

GGC G1y 285

GAA ATG

CAG Gln

GCC GAT CTG CGC GTC Ala Asp Leu Arg Val 305

GTC

GAA (

GGC

Asp 300 GAC

GTG Val

GGC GIY

GAT Asp

AAG Lys 220

GAC

ACC Thr

ATC Ile

CAG ACC .

GGC Gly

GTC Val 235

CTT Leu

CTG Leu

ATG Met

GAA Glu

ACC Thr

CAC His

AAG 1 Lys 1 205

| U.S. Pate | ent | May 27, 1 | 1997 | Sheet 12 o | of 70 | 5,63 | 3,435 |
|---|---|---|---|---|---|---|-----------|
| | | | | | | , | |
| 1072 | 1120 | 1168 | 1216 | 1264 | 1312 | 1360 | |
| CGT GCG CCG TCG ATG ATC GAC GAA TAT CCG Arg Ala Pro Ser Met Ile Asp Glu Tyr Pro 320 | TCC TTC GCG GAA GGC GAA ACC GTG ATG GAC Ser Phe Ala Glu Gly Glu Thr Val Met Asp 345 | GTC AAG GAA TCG GAT CGT CTG GCA GCG GTC Val Lys Glu Ser Asp Arg Leu Ala Ala Val 355 | AAC GGC GTC GAT TGC ACC GAA GGC GAG ATG Asn Gly Val Asp Cys Thr Glu Gly Glu Met 370 | CGC CCC GAC GGC AAG GGA CTG GGC GGC GGC Arg Pro Asp Gly Lys Gly Leu Gly Gly Gly 385 | GAT CAT CGT ATC GCG ATG AGC TTC CTC GTG Asp His Arg Ile Ala Met Ser Phe Leu Val 400 | AAG CCG GTG ACG GTT GAC GAC AGT AAC ATG Lys Pro Val Thr Val Asp Asp Ser Asn Met 420 | Figure 4D |
| CCG GAA Pro Glu | GCC GCC Ala Ala 335 | CTG CGC Leu Arg 350 | GAA GCC Glu Ala | CGC GGC Arg Gly | CAT CTC His Leu | GCG GAA Ala Glu 415 | |
| T CCG 1 Pro | ATT Ile | GAA Glu | CTT Leu 365 | GTT Val | ACC Thr | GCG Ala | · |
| GTC GTT Val Val 315 | CTG GCG Leu Ala | CTC GAC Leu Asp | CGC GGC Arg Gly | CTG ACG Leu Thr 380 | GTT GCA Val Ala 395 | GGC CTT Gly Leu | |
| GTC Val | GTC Val 330 | GGG G1y | GCA Ala | TCG | ACG | ATG Met 410 | |

| U.S. Patent | M | Iay 27, 1997 | | Sheet | 13 of | 70 | |
|-------------|---|--|---|---|--|------------------------------------|-----------|
| α Ο | 0 0 # H | 1462 | 1522 | 1582 | 1642 | 1673 | |
| | ATC GCC ACG TCC TTC CCC GAA TTC ATG GAC ATG CCG GGA TTG GGC Ile Ala Thr Ser Phe Pro Glu Phe Met Asp Met Met Pro Gly Leu Gly 435 | GCA AAG ATC GAG TTG AGC ATA CTC TAGTCACTCG ACAGCGAAAA TATTATTTGC Ala Lys Ile Glu Leu Ser Ile Leu 445 | GAGATIGGGC ATTATTACCG GTTGGTCTCA GCGGGGGTTT AATGTCCAAT CTTCCATACG | TAACAGCATC AGGAAATATC AAAAAAGCTT TAGAAGGAAT TGCTAGAGCA GCGACGCCGC | CTAAGCTTTC TCAAGACTTC GTTAAAACTG TACTGAAATC CCGGGGGGTC CGGGGAATCAA | ATGACTTCAT TTCTGAGAAA TTGGCCTCGC A | Figure 4E |

5,633,435

| U.S. | Patent |
|-------------|---------------|
| U.D. | 1 altill |

| Mav | 27. | 1997 |
|--------|-----|------|
| ****** | _,, | |

| Sheet | 14 | of | 70 |
|-------|----|----|----|
| | | | |

| 5,633,43 | 35 |
|----------|----|
| , | _ |

5A Figure

| 54 | 102 | 150 | 198 | 246 | 294 | 342 |
|--|--|--|---|--|--|--|
| GTGATCGCGC CAAAATGTGA CTGTGAAAAA TCC ATG TCC CAT TCT GCA TCC CCG Met Ser His Ser Ala Ser Pro 1 | AAA CCA GCA ACC GCC CGC TCG GAG GCA CTC ACG GGC GAA ATC CGC Lys Pro Ala Thr Ala Arg Arg Ser Glu Ala Leu Thr Gly Glu Ile Arg 10 | ATT CCG GGC GAC AAG TCC ATC TCG CAT CGC TCC TTC ATG TTT GGC GGT Ile Pro Gly Asp Lys Ser Ile Ser His Arg Ser Phe Met Phe Gly Gly 30 | CTC GCA TCG GGC GAA ACC CGC ATC ACC GGC CTT CTG GAA GGC GAG GAC Leu Ala Ser Gly Glu Thr Arg Ile Thr Gly Leu Leu Glu Gly Glu Asp 40 55 | GTC ATC AAT ACA GGC CGC GCC ATG CAG GCC ATG GGC GCG AAA ATC CGT Val 11e Asn Thr Gly Arg Ala Met Gln Ala Met Gly Ala Lys 11e Arg 60 | AAA GAG GGC GAT GTC TGG ATC ATC AAC GGC GTC GGC AAT GGC TGC CTG Lys Glu Gly Asp Val Trp Ile Ile Asn Gly Val Gly Asn Gly Cys Leu 85 | TTG CAG CCC GAA GCT GCG CTC GAT TTC GGC AAT GCC GGA ACC GGC GCG Leu Gln Pro Glu Ala Ala Leu Asp Phe Gly Asn Ala Gly Thr Gly Ala 90 |
| | | | | | | |

| U.S. Pate | Patent May 27, 1997 | | Sheet 15 | of 70 | 5,63 | 5,633,435 | |
|-------------------|---------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------|
| | | | | | | | |
| 390 | 438 | 486 | 534 | 282 | 630 | 678 | |
| | | | | | | | w 14 |
| TTT Phe | AAC Asn 135 | CGC Arg | тат Туг | GCC Ala | ACC Thr | ACG Thr 215 | |
| TCC | CTG | GAC ASP 150 | ACC Thr | CTC | ATG Met | CTC | · |
| ACC | GTG Val | GGC Gly | ATC Ile 165 | CTG Leu | GTC Val | gac Asp | 2B |
| AAG Lys | CGC Arg | GAT Asp | CCG | GTG Val | CCG | GCC Ala | |
| ATG Met 115 | GGC Gly | GCC Ala | AAT Asn | GCC Ala | GAG Glu 195 | GGC | Figure |
| GAC Asp | ATG Met 130 | GCA Ala | GCC Ala | TCC | ATC Ile | TTT Phe 210 | -i-g |
| TAT Tyr | CCG | GAA Glu 145 | ACG Thr | AAA Lys | GTC Val | GGC Gly | 124 |
| ACC Thr | CGC Arg | GTG Val | AAG Lys 160 | GTA Val | ACC Thr | CAG Gln | |
| GGC G1y | AAG Lys | CAG Gln | CCG | CAG Gln 175 | ACC Thr | CTG Leu | |
| GTC Val 110 | TCG | GTT Val | GGC Gly | GCG Ala | GTC Val 190 | ATG Met | |
| CTT Leu | CTG Leu 125 | GGC G1y | ATC Ile | TCC | GGC G1Y | AAG Lys 205 | |
| GGC | TCG Ser | ATG Met 140 | CTG | GCC Ala | CCG Pro | GAA Glu | |
| ATG Met | GCC Ala | GAA Glu | ACG Thr 155 | ATG Met | ACG Thr | ACC Thr | |
| ACC Thr | GAC Asp | CGC Arg | CTG | CCG Pro 170 | AAC Asn | CAC His | |
| CTC Leu 105 | GGC Gly | TTG | CCG | GTG Val | CTC Leu 185 | GAC Asp | |
| CGC | ATC I1e 120 | CCG | ATG Met | CGC Arg | GGT | CGC Arg 200 | |

| U.S. Pat | ent | May 27, | 1997 | Sheet 16 | of 70 | 5,6 | 33,435 |
|---|---|---|---|--|--|---|-----------|
| | | | · | | | | |
| 726 | 774 | 822 | 870 | 918 | 996 | 1014 | |
| GGC GTG CGC CAT ATC CGC ATC ACC GGC CAG Gly Val Arg His Ile Arg Ile Thr Gly Gln 225 | ACC ATC GAC GTG CCG GGC GAT CCG TCA TCG Thr Ile Asp Val Pro Gly Asp Pro Ser Ser 240 | GCC GCC CTT CTG GTG GAA GGT TCC GAC GTC Ala Ala Leu Leu Val Glu Gly Ser Asp Val 255 | ATG AAC CCG ACC CGT ACC GGC CTC ATC CTC Met Asn Pro Thr Arg Thr Gly Leu Ile Leu 270 | GCC GAT ATC GAA GTG CTC AAT GCC, CGT CTT Ala Asp Ile Glu Val Leu Asn Ala Arg Leu 295 | SCC GAT CTG CGC GTC AGG GCT TCG AAG CTC la Asp Leu Arg Val Arg Ala Ser Lys Leu 305 | cg gaa cgr gcg ccg rcg arg arc gac gaa ro Glu Arg Ala Pro Ser Met Ile Asp Glu 320 | Figure 5C |
| GTC GAG ACC GAC AAG GAT G Val Glu Thr Asp Lys Asp G | GGC AAG CTT GTC GGC CAG A Gly Lys Leu Val Gly Gln T 235 | ACC GCC TTC CCG CTC GTT G Thr Ala Phe Pro Leu Val A 250 | ACC ATC CGC AAC GTG CTG A Thr lle Arg Asn Val Leu M 265 | ACC TTG CAG GAA ATG GGC G Thr Leu Gln Glu Met Gly A 280 | GCA GGC GGC GAA GAC GTC G Ala Gly Gly Glu Asp Val A | AAG GGC GTC GTC GTT CCG C Lys Gly Val Val Val Pro F 315 | |

| S. Pate | ent | May 27, | 1997 | Sheet 17 | of 70 | 5,63 | 33,435 |
|---|---|---|---|---|---|---|-----------|
| 1062 | 1110 | 1158 | 1206 | 1254 | 1302 | 1350 | |
| G GTC CTG GCG ATT GCC GCC TCC TTC GCG GAA GGC GAA ACC GTG o Val Leu Ala Ile Ala Ala Ser Phe Ala Glu Gly Glu Thr Val 330 | C GGG CTC GAC GAA CTG CGC GTC AAG GAA TCG GAT CGT CTG GCA p Gly Leu Asp Glu Leu Arg Val Lys Glu Ser Asp Arg Leu Ala 355 | C GCA CGC GGC CTT GAA GCC AAC GGC GTC GAT TGC ACC GAA GGC 1 Ala Arg Gly Leu Glu Ala Asn Gly Val Asp Cys Thr Glu Gly 375 | G TCG CTG ACG GTT CGC GGC CGC CCC GAC GGC AAG GGA CTG GGC t Ser Leu Thr Val Arg Gly Arg Pro Asp Gly Lys Gly Leu Gly 380 | C ACG GTT GCA ACC CAT CTĊ GAT CAT CGT ATC GCG ATG AGC TTC y Thr Val Ala Thr His Leu Asp His Arg Ile Ala Met Ser Phe 395 | G ATG GGC CTT GCG GCG GAA AAG CCG GTG ACG GTT GAC GAC AGT 1 Met Gly Leu Ala Ala Glu Lys Pro Val Thr Val Asp Asp Ser 410 | G ATC GCC ACG TCC TTC CCC GAA TTC ATG GAC ATG ATG CCG GGA t Ile Ala Thr Ser Phe Pro Glu Phe Met Asp Met Met Pro Gly 5 | Figure 5D |
| TAT CCG Tyr Pro | ATG GAC Met Asp 345 | GCG GTC Ala Val 360 | GAG ATG Glu Met | GGC GGC Gly Gly | CTC GTG Leu Val | AAC ATG Asn Met 425 | |

| U.S. Patent | May 27, 1997 | | Sheet 1 | 8 of 70 |
|-------------|---|---|---|-----------|
| | 1400 | 1460 | 1500 | |
| | TTG GGC GCA AAG ATC GAG TTG AGC ATA CTC TAGTCACTCG ACAGCGAAAA Leu Gly Ala Lys Ile Glu Leu Ser Ile Leu 440 | TATTATTTGC GAGATTGGGC ATTATTACCG GTTGGTCTCA GCGGGGGTTT AATGTCCAAT | CTTCCATACG TAACAGCATC AGGAAATATC AAAAAAGCTT | Figure 5E |

5,633,435

년 년

```
144
                                                                                                                                                                                      147
                                                                                                                                                                                                                                                                                 197
                                                                                                                                                                                                                                                                                                                               194
                                                                                                                                                                                                                                                                                                                                                                            247
50
                                             44
                                                                                          98
                                                                                                                                         94
                                                                                                                                                                                                                                                                                                                                                                                                                           244
                                                                                                                                         LDSDDVRHMLNALTALGVSYTLSADRTRCEIIGNGGPLHAEGALELFLGN
                                                                                                                                                                                     AATGCRLTMGLVGVYDFDSTFIGDASLTKRPMGRVLNPLREMGVQVK.SE
                                                                                                                                                                                                                                   AGTAMRPLAAALCLGSNDIVLTGEPRMKERPIGHLVDALRLGGAKITYLE
                                             .....MESLTLQPIARVDGTINLPGSKTVSNRALLLAALAHGKTVLTNL
                                                                                                                                                                                                                                                                                                                                                                           MTRDHTEKMLQGFGANLTVETDADGVRTIRLEGRGKLTGQVIDVPGDPSS
                                                                                                                                                                                                                                                                     DGDRLPVTLRGPKTPTPITYRVPMASAQVKSAVLLAGLNTPGITTVIEPI
                                                                                                                                                                                                                                                                                                                                                                                                                          LVSKPYIDITLNLMKTFGVEIENQHYQQFVVKGGQSYQSPGTYLVEGDAS
MSHGASSRPATARKSSGLSGTVRIPGDKSISHRSFMFGGLASGETRITGL
                                                                                           LEGEDVINTGKAMQAMGARIRKEGDTWIIDGVGNGGLLAPEAPLD
                                                                                                                                                                                                                                                                                     148
                                                                                                                                                                                                                                                                                                                                                                                198
                                                                                                                                                                                                                                                                                                                                                                                                                              195
                                                                                                                                                                                                                                                                                                                                   145
                                                                                               51
                                                                                                                                              S
```

| 248 | TAFPLV | 295 |
|-----|--|-----|
| 245 | SASYFLAAAAIKGGTVKVTGIGRNSMQGDIRFADVLEKMGATI | 287 |
| 296 | AGGEDVADLRVRSSTLKGVTVPEDRAPSMIDEYPILAVAAAFAEGATVMN | 345 |
| 288 | . : :: .:. .:::: :: : . . . :. CWGDDYISCTRGELNAIDMDMNHIPDAAMTIATAALFAKGTTRLR | 332 |
| 346 | KESDRLSAVANGLKLNGVDCDEGETSLVVRGRPDGKGLGNASG | 395 |
| 333 | .: :: | 376 |
| 396 | 396 AAVATHLDHRIAMSFLVMGLVSENPVTVDDATMIATSFPEFMDLMAGLGA 445 | 145 |
| 377 | .: . : : ::: :. : : :::: : ::. 377 AEIATYNDHRMAMCFSLVAL.SDTPVTILDPKCTAKTFPDYFEQLARISQ 425 | 125 |
| 446 | KIELSDTKAA* 456 | |

Figure 7A

| ⊣ | ~ | 20 |
|-----|---|----------|
| · | : : : : : : | 50 |
| l | | 7 |
| 51 | LEGEDVINTGRAMQAMGARIRREGDIWIIDGVGNGGDDAFEAFDFGNAA |) |
| 51 | LEGEDVINTGRAMQAMGAKIRKEGDVWIINGVGNGCLLQPEAALDFGNAG | 100 |
| 101 | | 150 |
| | | |
| 101 | TGARLTMGLVGTYDMKTSFIGDASLSKRPMGRVLNPLREMGVQVEAADGD | 150 |
| | | Ċ |
| 151 | RLPVTLRGPKTPTPTTTYRVPMASAQVKSAVLLAGLNTFGTTTVTEFTMTR | 7 |
| | | 0 |
| 151 | RMPLTLIGPKTANPITYRVPMASAQVKSAVLLAGLNTPGVTTVLEPVMTK | 700 |
| , | | C |
| 201 | DHTEKMLOGFGANLTVETDADGVRTTRLEGRGKLTGQV1DVFGDFSSTAF | 700 |
| | | ! |
| 201 | DHTEKMLQGFGADLTVETDKDGVRHIRITGQGKLVGQTIDVPGDPSSTAF | 250 |
| | | |
| 251 | PLVAALLVPGSDVTILNVLMNPTRTGLILTLQEMGADIEVINPRLAGGED | 300 |
| | | (|
| 251 | PLVAALLVEGSDVTIRNVLMNPTRTGLILTLQEMGADIEVLNARLAGGED | 300 |

| 84 | CTCATCTTGA | AACGTTTTGA TGAACCCAAC CCGTACTGGT CTCATCTTGA | TGAACCCAAC | AACGTTTTGA | GTTCCGACGT CACCATCCTT | GTTCCGACGT |
|----|------------|--|---|-----------------------|---|------------|
| 78 | CTTGTTCCAG | TGCTGCCTTG | TGATCCATCC TCTACTGCTT TCCCATTGGT TGCTGCCTTG | TCTACTGCTT | | ATGTTCCAGG |
| 72 | CAAGTGATTG | GCTCACCGGT | GTCGTGGTAA | CGTCTTGAAG | CTGACGGTGT GCGTACCATC CGTCTTGAAG GTCGTGGTAA GCTCACCGGT CAAGTGATTG | CTGACGGTGT |
| 99 | GAGACTGATG | CCTTACCGTT | TTGGTGCTAA | CTTCAAGGTT | GTGACCACAC TGAAAAGATG CTTCAAGGTT TTGGTGCTAA CCTTACCGTT GAGACTGATG | GTGACCACAC |
| 09 | ATCATGACTC | TGGTCTCAAC ACCCCAGGTA TCACCACTGT TATCGAGCCA ATCATGACTC | TCACCACTGT | ACCCCAGGTA | | TTCTGCTTGC |
| 54 | AAGTCCGCTG | CGCTCAAGTG | CTATGGCTTC | TACAGGGTAC | AGACTCCAAC GCCAATCACC | AGACTCCAAC |
| 48 | CGTGGACCAA | AGTTACCTTG | ATCGTCTTCC | GAAGACGGTG | TGGGTGTGCA GGTGAAGTCT GAAGACGGTG ATCGTCTTCC AGTTACCTTG | TGGGTGTGCA |
| 42 | CTTCGCGAAA | GTTGAACCCA | TGGGTCGTGT | AAGCGTCCAA | TTGGTGACGC TTCTCTCACT AAGCGTCCAA TGGGTCGTGT GTTGAACCCA CTTCGCGAAA | TTGGTGACGC |
| 36 | AGCACTTTCA | CCGTTTGACT ATGGGTCTTG TTGGTGTTTA CGATTTCGAT AGCACTTTCA | TTGGTGTTTA | ATGGGTCTTG | | CAACTGGTTG |
| 30 | GGTAACGCTG | CTGAGGCTCC TCTCGATTTC GGTAACGCTG | | TAACGGIGGA CICCTIGCIC | | ATGGTGTTGG |
| 24 | TGGATCATTG | AGGTGATACT | TCCGTAAGGA | GGTGCCAGAA | GTAAGGCTAT GCAAGCTATG GGTGCCAGAA TCCGTAAGGA AGGTGATACT | GTAAGGCTAT |
| 18 | ATCAACACTG | TTTTGGAAGG TGAAGATGTT | TTTTGGAAGG | ATCACCGGTC | TCGCTAGCGG TGAAACTCGT ATCACCGGTC | TCGCTAGCGG |
| 12 | TTTGGAGGTC | TATTCCAGGT GACAAGTCTA TCTCCCACAG GTCCTTCATG TTTGGAGGTC | TCTCCCACAG | GACAAGTCTA | | GAACCGTCCG |
| Φ | GGTCTTTCTG | TAAGTCCTCT | CAACTGCTCG | AGCCGTCCAG | CCATGGCTCA CGGTGCAAGC AGCCGTCCAG CAACTGCTCG TAAGTCCTCT GGTCTTTCTG | CCATGGCTCA |

| U.S. Patent | | May : | 27, 199 | 97 | Sho | eet 24 | of 70 | | 5,633,435 |
|---|---|---|---|---|---|---|---|--|-----------|
| 006 | 960 | 1020 | 1080 | 1140 | 1200 | 1260 | 1320 | 1377 | ·. |
| SCC GACATCGAAG TGATCAACCC ACGTCTTGCT GGTGGAGAAG | STT CGTTCTTA CTTTGAAGGG TGTTACTGTT CCAGAAGACC | SAC GAGTATCCAA TTCTCGCTGT TGCAGCTGCA TTCGCTGAAG | BGT TTGGAAGAAC TCCGTGTTAA GGAAAGCGAC CGTCTTTCTG | AAG CTCAACGGTG TTGATTGCGA TGAAGGTGAG ACTTCTCTCG | 3AC GGTAAGGGTC TCGGTAACGC TTCTGGAGCA GCTGTCGCTA | ATC GCTATGAGCT TCCTCGTTAT GGGTCTCGTT TCTGAAAACC | SCT ACTATGATCG CTACTAGCTT CCCAGAGTTC ATGGATTTGA | AAG ATCGAACTCT CCGACACTAA GGCTGCTTGA TGAGCTC | Figure 8B |
| AATGGGI | CTTGCGI | TATGATC | TATGAAC | CGGTCTC | TCGTCCI | TCACCGI | TGATGAT | TGGAGCI | |
| CTCTGCAGGA AATGGGTGCC GACA | ACGIGGCIGA CITGCGIGIT CGIT | STGCTCCTTC TATGATCGAC GAGT | GTGCTACCGT TATGAACGGT TTGG | CTGTCGCAAA CGGTCTCAAG CTCA | TCGTGCGTGG TCGTCCTGAC GGTA | CCCACCTCGA TCACCGTATC GCTA | CTGTTACTGT TGATGATGCT ACTA | TGGCTGGTCT TGGAGCTAAG ATCG | |

| U.S. I | Patent | May 2 | 7, 1997 | Sheet 25 | of 70 | 5,63 | 3,43 |
|---|--|--|--|--|--|--|----------|
| 09 | 113 | 161 | 209 | 257 | 305 | 318 | |
| AGATCTATCG ATAAGCTTGA TGTAATTGGA GGAAGATCAA AATTTTCAAT CCCCATTCTT | CGATTGCTTC AATTGAAGTT TCTCCG ATG GCG CAA GTT AGC AGA ATC TGC AAT Met Ala Gln Val Ser Arg Ile Cys Asn 1 | GGT GTG CAG AAC CCA TCT CTT ATC TCC AAT CTC TCG AAA TCC AGT CAA Gly Val Gln Asn Pro Ser Leu Ile Ser Asn Leu Ser Lys Ser Ser Gln 10 | CGC AAA TCT CCC TTA TCG GTT TCT CTG AAG ACG CAG CAT CCA CGA Arg Lys Ser Pro Leu Ser Val Ser Leu Lys Thr Gln Gln His Pro Arg 30 | GCT TAT CCG ATT TCG TCG TCG TGG GGA TTG AAG AAG AGT GGG ATG ACG Ala Tyr Pro Ile Ser Ser Trp Gly Leu Lys Lys Ser Gly Met Thr 50 | TTA ATT GGC TCT GAG CTT CGT CCT CTT AAG GTC ATG TCT TCT GTT TCC Leu lle Gly Ser Glu Leu Arg Pro Leu Lys Val Met Ser Ser Val Ser 60 | ACG GCG TGC ATG C Thr Ala Cys Met 75 | Figure 9 |

| U.S. Patent | Мау | y 27, 1997 | Sheet 26 | 5 of 70 | 5,633,435 |
|---|--|--|--|--|------------|
| 09 | 113 | 161 | 209 | 257 | |
| AGATCTATCG ATAAGCTTGA TGTAATTGGA GGAAGATCAA AATTTTCAAT CCCCATTCTT | CGATTGCTTC AATTGAAGTT TCTCCG ATG GCG CAA GTT AGC AGA ATC TGC AAT Met Ala Gln Val Ser Arg Ile Cys Asn 1 | GGT GTG CAG AAC CCA TCT CTT ATC TCC AAT CTC TCG AAA TCC AGT CAA Gly val Gln Asn Pro Ser Leu Ile Ser Asn Leu Ser Lys Ser Ser Gln 10 | CGC AAA TCT CCC TTA TCG GTT TCT CTG AAG ACG CAG CAT CCA CGA Arg Lys Ser Pro Leu Ser Val Ser Leu Lys Thr Gln Gln His Pro Arg 30 | GCT TAT CCG ATT TCG TCG TCG TGG GGA TTG AAG AAG AGT GGG ATG ACG Ala Tyr Pro Ile Ser Ser Trp Gly Leu Lys Lys Ser Gly Met Thr 50 | Figure 10A |

| U.S. Patent | May | 27, 1997 | Sheet 27 | of 70 |
|-------------|------------------|------------------|-------------------|-------|
| ر د د | O | 353 | 401 | 402 |
| | | | | |
| ζ (| Ser | ATC Ile | ATT 11e 105 | |
| E E | GIT. Val | GAA Glu | AGA Arg | |
| E Ç E | Ser | AGA Arg | AAT Asn | 10B |
| Ë | ser 70 | ATT Ile | TCA Ser | |
| C E | AT'G Met | CCC Pro 85 | CTA Leu | ıre |
| E | Gr.C Val | CAA Gln | TCT Ser 100 | igure |
| (F F | AAG Lys | CTT Leu | AAG Lys | Ţ |
| E | CT"I Leu | GTA Val | TCC Ser | |
| · E | CCT Pro 65 | ATT Ile | GGC Gly | |
| | CGT Arg | GAG G1u 80 | CCT Pro | |
| | CTT | TCG | TTG Leu 95 | |
| | GAG Glu | GCG Ala | AAG Lys | |
| | TCT Ser | AAA Lys | ATT Ile | |
| | GGC G1y 60 | GAG Glu | CTT Leu | |
| | ATT Ile | GCG Ala 75 | GGT Gly | |
| | TTA | ACG Thr | TCC Ser 90 | υ |
| | | | | |

5,633,435

| U.S. Patent | May 27, 1997 | | Sheet 28 of 70 | | 5,633,435 |
|--|--|--|--|--|-----------|
| 4 | . 6 | 145 | 193 | 233 | |
| AGATCTTTCA AGA ATG GCA CAA ATT AAC AAC ATG GCT CAA GGG ATA CAA Met Ala Gln Ile Asn Asn Met Ala Gln Gly Ile Gln 1 | ACC CTT AAT CCC AAT TCC CAT AAA CCC CAA GTT CCT AAA TCT Thr Leu Asn Pro Asn Ser Asn Phe His Lys Pro Gln Val Pro Lys Ser 15 | TCA AGT TTT CTT TTT GGA TCT AAA AAA CTG AAA AAT TCA GCA AAT Ser Ser Phe Leu Val Phe Gly Ser Lys Lys Leu Lys Asn Ser Ala Asn 30 | TCT ATG TTG GTT TTG AAA AAA GAT TCA ATT TTT ATG CAA AAG TTT TGT Ser Met Leu Val Leu Lys Lys Asp Ser Ile Phe Met Gln Lys Phe Cys 45 | TCC TTT AGG ATT TCA GCA TCA GTG GCT ACA GCC TGC ATG C Ser Phe Arg Ile Ser Ala Ser Val Ala Thr Ala Cys Met 65 | Figure 11 |

| U.S. Patent | May 27, 1997 | Shee | t 29 of 70 | 5,633,435 |
|--|---|--|--|------------|
| 57 | 105 | 153 | 201 | |
| AGATCTGCTA GAATTATT TGTTTAACTT TAAGAAGGAG ATATATCC ATG GCA CAA | ATT AAC AAC ATG GCT CAA GGG ATA CAA ACC CTT AAT CCC AAT TCC AAT Ile Asn Asn Met Ala Gln Gly Ile Gln Thr Leu Asn Pro Asn Ser Asn 5 | TTC CAT AAA CCC CAA GTT CCT AAA TCT TCA AGT TTT CTT GTT TTT GGA Phe His Lys Pro Gln Val Pro Lys Ser Ser Ser Phe Leu Val Phe Gly 20 | TCT AAA AAA CTG AAA AAT TCA GCA AAT TCT ATG TTG GTT TTG AAA AAA Ser Lys Lys Leu Lys Asn Ser Ala Asn Ser Met Leu Val Leu Lys Lys 45 | Figure 12A |

| U.S. Patent | May 27, 1997 | Shee | et 30 of 70 | 5,633,435 |
|------------------|------------------|------------------|-------------------|-----------|
| 249 | 297 | 345 | 352 | |
| TCA | AAA Lys | AAT Asn | | |
| GCA | ATT Ile | TCT Ser | | |
| TCA Ser 65 | CCC | TTA Leu | | 12B |
| ATT Ile | CAA Gln 80 | TCA | | |
| AGG | TTG Leu | AAA Lys 95 | | ıre |
| TTT Phe | GTG Val | TCT Ser | | igure |
| JCC Ser | ATA Ile | GGC Gly | | <u>F</u> |
| TGT Cys | | CCT Pro | | |
| TTT Phe | TCT Ser 75 | TTG Leu | | |
| AAG Lys | CCT | AAA Lys 90 | | |
| CAA | AAG Lys | GTT Val | | |
| ATG Met | CAG Gln | ACT Thr | | |
| TTT Phe 22 |) < 0 | GGC Gly | | |
| ATT Ile | ACA Thr 70 | TCA Ser | U | |
| TCA | GCT Ala | ATT Ile 85 | ATT Ile | |
| GAT | GTG Val | GAG | AGA Arg 100 | |

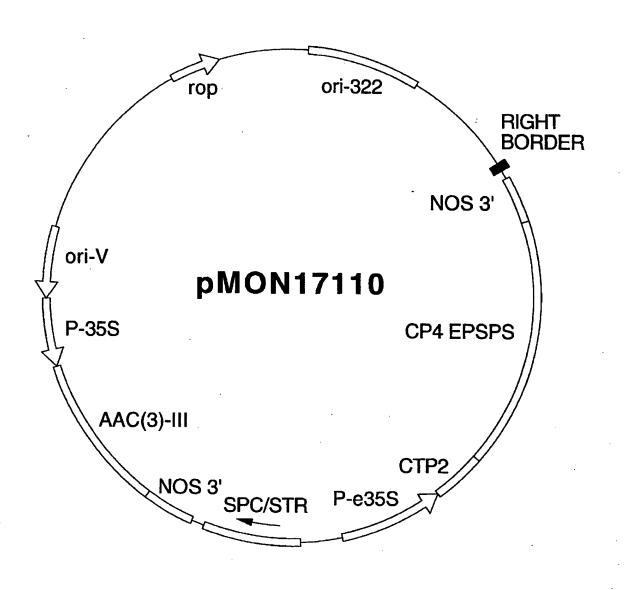
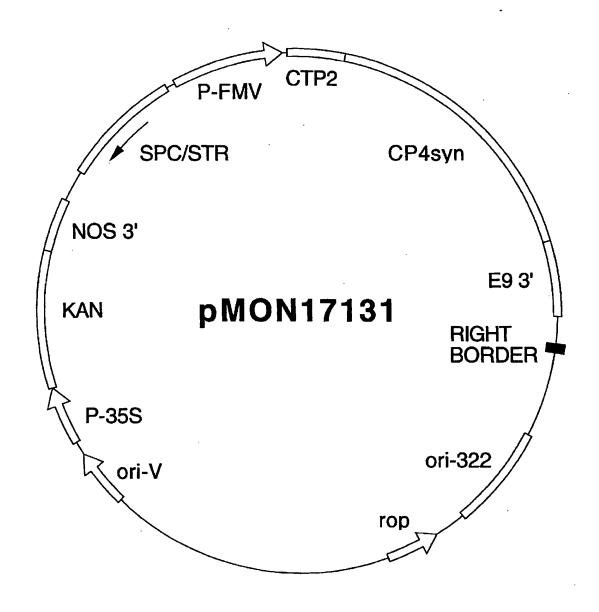


Figure 13



Figure

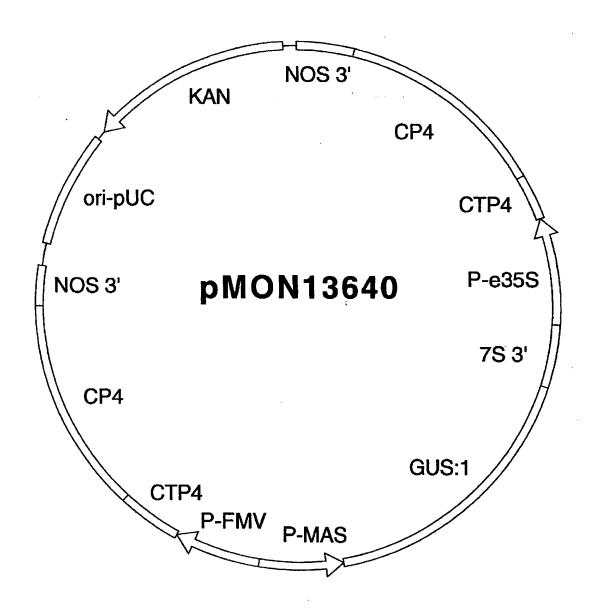


Figure 15

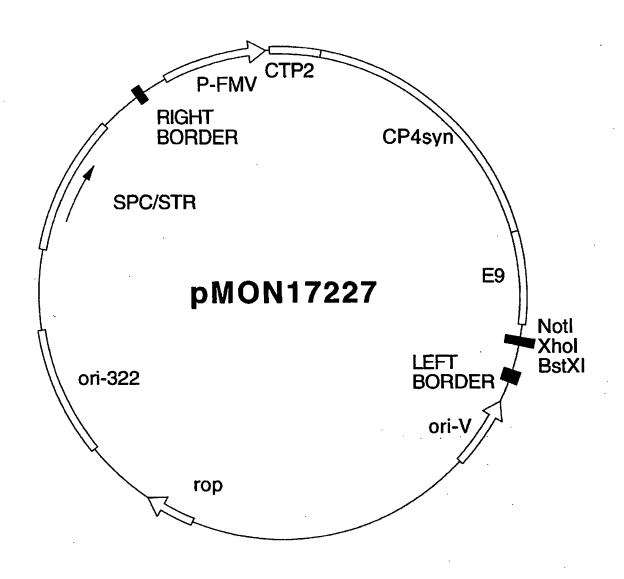


Figure 16

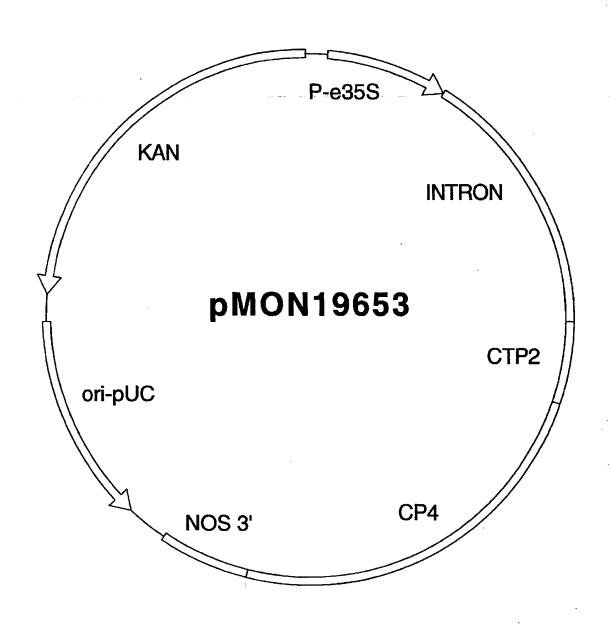


Figure 17

| U.S. Pat | ent | May 27, 1997 | | Sheet 36 of 70 | | 5,633,435 | |
|--|--|--|--|--|--|---|------------|
| 4 . | 96 | 144 | 192 | 240 | 288 | 336 | |
| ACC TTA CAT GGA GAA ATA CAT ATT CCC Thr Leu His Gly Glu Ile His Ile Pro 10 | CGC TCT GTT ATG TTT GGC GCG CTA GCG Arg Ser Val Met Phe Gly Ala Leu Ala 25 | AAC TTT CTG CCG GGA GCA GAT TGT CTG Asn Phe Leu Pro Gly Ala Asp Cys Leu 40 | AAA ATG GGT GTT CAC ATT GAG CAA AGC Lys Met Gly Val His Ile Glu Gln Ser 60 | GGA AAA GGA ATC GAT GCC CTG AAA GAG Gly Lys Gly Ile Asp Ala Leu Lys Glu 75 | GGA AAT TCA GGT ACA ACG ATT CGC CTG Gly Asn Ser Gly Thr Thr Ile Arg Leu 90 | CGT CCT TTT TAC AGC GCG GTA GCC GGA Arg Pro Phe Tyr Ser Ala Val Ala Gly 105 | Figure 18A |

GTG ATT CAC G Val Ile His G

AGC GAT GTC Ser Asp Val

AGC Ser 65

G1y

Ala

Leu

ATG CTC GGA ATA T Met Leu Gly Ile L 100

TIG GCG GGC

TTA GAT GTC (Leu Asp Val (85

CTT

GAA AGC (Glu Ser]

CCA

ACA GTT AAA AAC TTT CTG Thr Val Lys Asn Phe Leu 40

ACA Thr

ACA Thr Thr 35

GGC Gly

GCA Ala

TTT AGA

Phe Arg I

ACG ATC GAT TGC T Thr Ile Asp Cys P

AGC

Ser

AAA CGA GAT AAG GTG CAG ACC Lys Arg Asp Lys Val Gln Thr 5

ATG Met

ATT TCT CAC

JCC

Ser His

Ile

Ser

GGT GAT AAA Gly Asp Lys

| U.S. Pate | ent | May 27, | 1997 | Sheet 37 | of 70 | 5,63 | 33,435 |
|---|---|---|---|---|---|---|------------|
| 384 | 432 | 480 | 528 | 576 | 624 | 672 | |
| GAT GAG AGC ATT GCG AAA CGC CCA ATG AAG CGT GTG ACT GAG CCT TTG ASP Glu Ser Ile Ala Lys Arg Pro Met Lys Arg Val Thr Glu Pro Leu 126 | AAA AAA ATG GGG GCT AAA ATC GAC GGC AGA GCC GGC GGA GAG TTT ACA Lys Lys Met Gly Ala Lys Ile Asp Gly Arg Ala Gly Gly Glu Phe Thr 130 | CCG CTG TCA GTG AGC GGC GCT TCA TTA AAA GGA ATT GAT TAT GTA TCA Pro Leu Ser Val Ser Gly Ala Ser Leu Lys Gly Ile Asp Tyr Val Ser 145 | CCT GTT GCA AGC GCG CAA ATT AAA TCT GCT GTT TTG CTG GCC GGA TTA Pro Val Ala Ser Ala Gln Ile Lys Ser Ala Val Leu Leu Ala Gly Leu 175 | CAG GCT GAG GGC ACA ACA ACT GTA ACA GAG CCC CAT AAA TCT CGG GAC Gln Ala Glu Gly Thr Thr Thr Val Thr Glu Pro His Lys Ser Arg Asp 180 | CAC ACT GAG CGG ATG CTT TCT GCT TTT GGC GTT AAG CTT TCT GAA GAT His Thr Glu Arg Met Leu Ser Ala Phe Gly Val Lys Leu Ser Glu Asp 200 | CAA ACG AGT GTT TCC ATT GCT GGT GGC CAG AAA CTG ACA GCT GCT GAT Gln Thr Ser Val Ser Ile Ala Gly Gly Gln Lys Leu Thr Ala Ala Asp 210 | Figure 18B |

| U.S. Pate | ent | May 27, 1 | 997 | Sheet 38 o | £ 70 | 5,63 | 3,435 |
|---|---|---|---|---|---|---|------------|
| 720 | 768 | 816 | 864 | 912 | 096 | 1008 | |
| TCT TCA GCC GCG TTT TTC CTT GCT GCT Ser Ser Ala Ala Phe Phe Leu Ala 235 | AGA ATT GTA TTG AAA AAC GTA GGT TTA Arg lle Val Leu Lys Asn Val Gly Leu 250 | ATT GAT GTC CTT CAA AAC ATG GGG GCA Ile Asp Val Leu Gln Asn Met Gly Ala 265 | GCT GAT AGC GGT GCA GAG CCT TAT GGA Ala Asp Ser Gly Ala Glu Pro Tyr Gly 280 | TCT CTA AAG GCA GTT GAA ATC GGA GGA Ser Leu Lys Ala Val Glu Ile Gly Gly 300 | GAT GAG ATC CCT ATC ATC GCG CTT CTT Asp Glu ile Pro ile ile Ala Leu Leu 315 | ACC GTT ATT AAG GAC GCG GCA GAG CTA Thr Val Ile Lys Asp Ala Ala Glu Leu 330 | Figure 18C |

AGC Ser

AAC Asn

CCA Pro 245

GTT Val

GCG ATG Ala Met

GGC Gly

ATTIle

GAC Asp 230

CCT GGA Pro Gly

GTT Val

TTT (Phe

ATT 11e 225

ATT A

GGT

ACA

Gly

CGG Arg 260

CCG ACT Pro Thr

AAT

TCT

CCA Pro

AAA (Lys

ATC Ile

GAA

CTTLeu

AAA Lys

Glu 275

TCA Ser 295

ACG

GAA

ATA Ile

ATT Ile

TTG Leu 290

GAT Asp

Ile

Leu 310

Pro Arg

ATT GAT

TTA

CGT

CCG

ATT Ile

ATC

GAT Asp 305 ACC 7

GGA 7

CAG GCG

ACT Thr

GCG

GAA Glu 325

| U.S. Pa | tent | May 27, 1997 | Shee | t 39 of 70 | 5,6 | 33,435 |
|------------|-------------------|---------------------------|-------------------|-------------------|-------------------|--------|
| 1056 | 1104 | 1152 | 1200 | 1248 | 1287 | |
| CGC | TAT TYr | GAT Asp | GAG Glu 400 | ACC | | |
| CTT Leu | GTT Val | GGA G1y | GAG Glu | CCA Pro 415 | | |
| GAG Glu | 350 AAG Lys | CAC | ACG Thr | TAT Tyr | | 18D |
| TCT Ser | ATG Met | 365 AGC Ser | ATA Ile | TCT | TGA | |
| GTT Val | GGA Gly | TCC Ser 380 | TGT Cys | GTT Val | TCC Ser | Figure |
| GTT Val | GAT Asp | GTG Val | TCC Ser 395 | CAC | AAA Lys | i.gr |
| ACT Thr | GCA Ala | GCA Ala | GCT Ala | ATT Ile 410 | AAA Lys | Īτι |
| GAT Asp | | GCT Ala | ATT Ile | GCC Ala | TCG Ser 425 | |
| ATT | CCG | 60 GC 14 | GGT G1y | GAT Asp | CTT Leu | |
| CGT | GAA Glu | GGC G1 <u>y</u> 375 | CTT | ACG Thr | AAG Lys | |
| AAC Asn | ATT Ile | AAA Lys | ATG Met 390 | CAC His | AAT Asn | |
| ACA Thr | GAA Glu | TTG | ATG Met | GAG Glu 405 | TTA Leu | |
| | 340 GCT Ala | | GGA Gly | ATC Ile | CAT His 420 | |
| AAA Lys | | | ATC Ile | GAA Glu | GAG Glu | |
| GTG | | | CGA | ATT Ile | TTC Phe | |
| AAA Lvs | | | CAT His 385 | | TTC Phe | |

| U.S. Pater | nt |
|------------|----|
|------------|----|

| May | 27, | 1997 |
|-----|-----|------|
|-----|-----|------|

| Sheet | 4 0 | οf | 70 |
|-------|------------|-----|----|
| SHEEL | 40 | OI. | /U |

| May 27, 1997 | Sheet 40 of 70 | 5,633,435 |
|--------------|----------------|-----------|
| | • | |

19A

Figure

| 48 | 96 | 144 | 192 | 240 | 288 | 336 |
|--------------------|------------------|--------------------|------------------------|------------------|------------------------|--------------------------|
| • | | | | | | |
| GAA Glu | TTG | GGC Gly | GAA Glu | CAA Gln 80 | ACA Thr | GTT Val |
| GGC Gly 15 | ATG Met | CTT Leu | GTA Val | \mathtt{TAT} | ACG Thr 95 | AGT Ser |
| AAG Lys | ATC I1e 30 | CTA | $_{\rm GLY}^{\rm GGT}$ | GGA Gly | $_{\rm G1y}^{\rm GGT}$ | GAA Glu 110 |
| TTA Leu | GCA Ala | CCA Pro 45 | TTA Leu | CCA | TCT Ser | AAT Asn |
| CCG | CGT Arg | AAG Lys | CAC His 60 | TCC | AAT | GGT Gly |
| GGT Gly | CAC His | TAT TY <i>r</i> | CGA Arg | ACT Thr 75 | GGT Gly | TTA Leu |
| TCA Ser 10 | ACA Thr | ATA Ile | TTC Phe | GTG Val | ACA Thr 90 | GGT Gly |
| ATT Ile | ATG Met 25 | ACT Thr | ATT Ile | GTT Val | TAT Tyr | AGT Ser 105 |
| GAT Asp | TCA | TCT Ser 40 | GAC Asp | TTA Leu | TTG | TTA |
| ATT Ile | AAG Lys | GTA Val | ATG Met 55 | AAA Lys | GTA Val | TTG |
| ATC Ile | GAT Asp | GGT Gly | ACG Thr | GAA Glu 70 | CAA Gln | GGT |
| CAA Gln 5 | GGC Gly | GAA Glu | CGT Arg | GAT Asp | CAT His 85 | GCA Ala |
| GAA Glu | CCG Pro 20 | GCT Ala | CGT Arg | GAT Asp | CCA Pro | TTG Leu |
| AAT Asn | GTG Val | CTA Leu 35 | TGT | GAA Glu | AAC ACG Asn Thr | CGA TTA Arg Leu |
| GTA Val | GAA Glu | TCG Ser | GAT Asp 50 | AAA Lys | | |
| ATG GTA Met Val | ATA Ile | GCG Ala | GAA Glu | ATC Ile 65 | GTT Val | ACA Thr |
| | | | | | | |

| U.S. Pater | nt | May 27, 1 | 997 | Sheet 41 o | f 70 | 5,63 | 3,435 |
|---|---|---|---|---|---|---|------------|
| 384 | 432 | 480 | 528 | 576 | 624 | 672 | |
| TTG TCT GGC GAT GTT TCA ATT GGT AAA AGG CCA ATG GAT CGT GTC TTG Leu Ser Gly Asp Val Ser Ile Gly Lys Arg Pro Met Asp Arg Val Leu 115 | AGA CCA TTG AAA CTT ATG GAT GCG AAT ATT GAA GGT ATT GAA GAT AAT Arg Pro Leu Lys Leu Met Asp Ala Asn Ile Glu Gly Ile Glu Asp Asn 130 | TAT ACA CCA TTA ATT ATT AAG CCA TCT GTC ATA AAA GGT ATA AAT TAT Tyr Thr Pro Leu Ile Ile Lys Pro Ser Val Ile Lys Gly Ile Asn Tyr 145 | CAA ATG GAA GTT GCA AGT GCA CAA GTA AAA AGT GCC ATT TTA TTT GCA Gln Met Glu Val Ala Ser Ala Gln Val Lys Ser Ala Ile Leu Phe Ala 170 | AGT TTG TTT TCT AAG GAA CCG ACC ATC ATT AAA GAA TTA GAT GTA AGT Ser Leu Phe Ser Lys Glu Pro Thr Ile Ile Lys Glu Leu Asp Val Ser 180 | CGA AAT CAT ACT GAG ACG ATG TTC AAA CAT TTT AAT ATT CCA ATT GAA Arg Asn His Thr Glu Thr Met Phe Lys His Phe Asn Ile Pro Ile Glu 195 | GCA GAA GGG TTA TCA ATT AAT ACA ACC CCT GAA GCA ATT CGA TAC ATT Ala Glu Gly Leu Ser Ile Asn Thr Thr Pro Glu Ala Ile Arg Tyr Ile 210 | Figure 19B |

| U.S. Pate | ent | May 27, 1 | 997 | Sheet 42 o | f 70 | 5,63 | 3,435 |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------|
| | | | | | | | |
| 720 | 768 | 816 | 864 | 912 | 096 | 1008 | |
| · | | , | | | * | | |
| TTC Phe 240 | CAT His | GAA Glu | GAA Glu | ATA Ile | GTA Val 320 | GAT Asp | |
| GCG Ala | ATT Ile 255 | GTT Val | GCT | CCA Pro | CCT | AAA Lys 335 | |
| GCA Ala | ACA Thr | ATT Ile 270 | GGT G1y | CAA Gln | CTG | ATT Ile | 19C |
| TCT Ser | GTA Val | GAT Asp | ACT Thr 285 | CTT | GAA Glu | ACA Thr | |
| TCA | GAT Asp | ATT Ile | ACA Thr | ATG Met 300 | GAT Asp | AGT Ser | ıre |
| ATT Ile 235 | AGT Ser | ATT Ile | CAA Gln | CCA Pro | ATT Ile 315 | ACG Thr | igure |
| GAT Asp | GGA G1Y 250 | GGT Gly | AAT | ACA Thr | GCA Ala | GGC G1y 330 | [E4 |
| GGC Gly | CCA | TCA Ser 265 | TTC Phe | TAC Tyr | AAA Lys | GTT Val | |
| CCT | ACA Thr | CGT Arg | CTT Leu 280 | CAA Gln | CCA Pro | GCA Ala | |
| GTT Val | ATC Ile | ACA Thr | CAA Gln | АТТ 11е 295 | GTT Val | CAA Gln | |
| CAT His 230 | CTT Leu | CAA Gln | ATC Ile | CGT Arg | TTA Leu 310 | ACA Thr | |
| TTT Phe | GCA Ala 245 | AAT Asn | AAT Asn | ATT Ile | GAA Glu | TGT Cys 325 | |
| GAT Asp | GCA Ala | ATC 11e 260 | GGT G1y | TCT Ser | GGA Gly | CTT Leu | |
| GCA Ala | GTT Val | GGA Gly | GGC Gly 275 | GCT Ala | GAA Glu | TTA | |
| CCT | ATT Ile | GTT Val | ATG Met | ACT Thr 290 | ATC Ile | GCA Ala | |
| AAA Lys 225 | TTT Phe | AAT | AAA Lys | CCT | ACA Thr 305 | ATA Ile | |

| U.S. Paten | t M | ay 27, 1997 | Sheet | 43 of 70 | 5,6 | 33,435 |
|---|---|---|---|---|---|------------|
| 1056 | 1104 | 1152 | 1200 | 1248 | 1293 | |
| A GTA AAA GAA AAT AGA ATT GAT ACA ACG GCT | G TTA GGG TTT GAA TTA CAA CCA ACT AAT GAT GGA | G TCA GAA TTT AAA ACA AAT GCA ACA GAT ATT TTA | A GGA ATG ATG CTT GCA GTT GCT TGT GTA CTT TCA | A ATC AAA CAA TTT GAT GCT GTA AAT GTA TCA TTT | A AAA CTA AAG CTT TTA CAA AAT GAG GGA TAA | Figure 19D |
| s Val Lys Glu Thr Asn Arg Ile Asp Thr Thr Ala | u Leu Gly Phe Glu Leu Gln Pro Thr Asn Asp Gly | o Ser Glu Phe Lys Thr Asn Ala Thr Asp Ile Leu | e Gly Met Met Leu Ala Val Ala Cys Val Leu Ser | s ile Lys Gln Phe Asp Ala Val Asn Val Ser Phe | o Lys Leu Lys Leu Leu Gln Asn Glu Gly | |
| 345 | 360 | 375 | 390 | 415 | 425 | |
| GCC GAG GAA TTA AAA | GAT ATG TTA AAC TTG | TTG ATT ATT CAT CCG | ACT GAT CAT CGA ATA | AGC GAG CCT GTC AAA | CCA GGA TTT TTA CCA | |
| Ala Glu Glu Leu Lys | Asp Met Leu Asn Leu | Leu Ile Ile His Pro | Thr Asp His Arg Ile | Ser Glu Pro Val Lys | Pro Gly Phe Leu Pro | |
| 340 | 355 | 370 | 385 | 405 | 420 | |

| | \leftarrow | | | 20 |
|--|---------------|----------|------------|----------------------------|
| PG2982 | • | | MSHSASPKPA | TARRSEALTG |
| L'BAA | • | | MSHSASPKPA | TARRSEALTG |
| Agrobacterium CP4 | | | MSHGASSRPA | TARKSSGLSG |
| B subtilis | | | M | KRDKVQTLHG |
| S. aureus | | | MVNEQ | IIDISGPLKG |
| S. Cerevisiae | • | | LVYP | FKDIPADQQK |
| A nidulans | | | VHP. | GVAHSSNV |
| B. naous | | | .KASEI | VLQPIREISG |
| A. thaliana | | | .KASEI | VLQPIREISG |
| N tabacum | • | | .KPNEI | VLQPIKDISG |
| I. esculentum | | | .KPHEI | VLXPIKDISG |
| p hybrida | | | .KPSEI | VLQPIKEISG |
| Syem 2 | | | AGAEEI | VLQPIKEISG |
| Translation of the second seco | | | MESL | TLQPIARVDG |
| | | | MESL | TLQPIARVDG |
| ۲ ۲ | | | MESL | TLOPIARVDG |
| | | | MESL | TLOPIARVDG |
| X nnelmoniae | | | MESL | TLOPIARVDG |
| Y entoercolitica | • | | MLESL | TLHPIALING |
| | • | | MEKI | TLAPISAVEG |
| P. miltocida | • | | MIKDATAI | TLNPISYIEG |
| A salmonicida | • | | NSI | RLEPISRVAG |
| B. pertussis | • | | MSGLAYL | DLPAARLARG |
| Consensus | 1 1 1 1 1 1 1 | 1 | | 1 1 1 1 1 1 |
| | | Figure 2 | 20A | |

RAMQAM.GAK RAMQAM.GAK KAMQAM.GAR DCFRKM.GVH DIFRHL. GVE TAVHELKGAT NALERLGAAT DALKKL.GLN DALKRL, GLN GALKTL. GLH GALKTL. GLH GALKTL. GLH GALRTL.GLS NALSAL.GIN NALSAL.GIN NALSAL.GIN NALTAL, GVS NALSAL. GVH NALOAL. GVK NALKAL. GVR LNSDDINYML LNSDDINYML LDSDDIRHML LHSDDTEVML LSSDDIHYML LDSDDVRHML LDSDDVRHML LDSDDVRHML LDSDDTRVML LLGEDCRRTM LHSDDTKHML LSSDDIHYML LDSDDVRHML LDSDDVRHML LDSDDIRHML LDSDDVRHML LEGEDVINTG LEGEDVINTG LPGADCLSTI LSSDDIHYML LNSEDVHYML LDSDDIRHML SEGTTVVDNL AEGVSTIYKP SEGTTVVDNL SEGTTVVDNL SKGRTVVDNL SEGRTVVDNL SEGTTVVDNL ACGKTVLTNL PCGKTALTNL ACGKTVLTNL AHGKTVLTNL AEGTTQLNNL AKGTTKVTNL AKGKTTLTNL ARGTTRLTNL AEGSTEITGL ASGETRITGL GEGQCKIKNL GSGTCRIKNL ARGTTVLTNL ASGETRITGL ASGETRITGL THRAIMLASL SNRALLLAAL SNRALLLAAL SNRALLLAAL SNRALLLAAL SNRALLLAAL SNRALLLSAL SNRALLLAAL SHRSFMFGGL SHRSVMFGAL SNRALVLAAL SNRILLLAAL SNRALLLAAL SNRALLLAAL SNRVLLLAAL SNRALILAAL SNRILLLAAL SNRILLLAAL SNRILLLAAL SNRILLLAAL SNRILLLAAL SHRSFMFGGL SHRSFMFGGL LIKLPGSKSL LIKLPGSKSL TVKLPGSKSL TVKLPGSKSL AINLPGSKSV AINLPGSKSV EIEVPGDKSM TVKLPGSKSL IVKLPGSKSL AINLPGSKSV **LINLPGSKTV** TVNLPGSKSV TVNLPGSKSV LINLPGSKSL EVRLPGSKSL EIRIPGDKSI EIRIPGDKSI EIHIPGDKSI WIPPGSKSI ICAPPGSKSI TVRIPGDKSI coli LBAA pneumoniae entoercolitica H. influenzae P. multocida salmonicida pertussis subtilis S. aureus cerevisiae nidulans B. napus thaliana tabacum esculentum P. hybrida Z. mays gallinarum typhimurium Consensus Agrobacterium CP4 PG2982 z ω . ×

RLMLGILAGR RLLAGLLSGL RFLTSLAALV RFLTTVATLA RPLTAAVTAA RPLTAAVTVA RPLTAAVTVA RLTMGLVGTY RPLTAAVTAA RPLTAAVTAA RPLAAALCL RPLAAALCL RPLAAALCL RPLAAALCL RPLAAALCL RPLAAALCL LYLGNAGTAM LFLGNAGTAM LDFGNAGTGA LYTGNSGTTT LYLGNAGTAS LYLGNAGTAM LFLGNAGTAM LFLGNAGTAF LDFGNAGTGA LYLGNAGTAS LFLGNAGTAM L--GN--T--GALE SALE ASIDSKSDIE VGKKSEEEIQ VGKKSEEEIQ VGKESKEEIQ VE.DAKEEVQ AP....GALE AP...GALE AE...QPLE ...SGLA ...APVN TE....QAE P....EAP P....ESL STLSACADP ..NLQASSSP ASLDSKSDIE AS...GTLE ...DNLS IVEGCGGOFP IVEGCGGOFP VVEGCGGLFP DITGNGGPLR VVEGCGGIFP WVGCGGKFP DITGNGGALR EIEGLGGAFN TVHGLGRSFA VVEGCGGIFP DITGNGGPLR EIIGNGGPLH NGVGNGCLLQ NGVGNGCLLQ HGKGIDALKE TSPGYQ.VNT VVEGHGG... WWNGKGG... EVTGTGGPLQ EVDGLGGKLV VEEDSANORA **VEADKAAKRA** FSWEEEGEVL VERDSVNNRA VEDDNENQRA /EDDNENORA VETDSENNRA /TLSADRTRC TLSADRTRC TLSADRTRC IRKEGDVWII IKEDDEKLVV TLSADRTRC YVLSSDRTRC RLSADRTRC YQLSDDKTIC IRKEGDVWII IRKEGDTWII IEQSSSDVVI ISWEDNGETV YKLSADKTEC gallinarum typhimurium pneumoniae H. influenzae P. multocida salmonicida pertussis Consensus Agrobacterium CP4 B. subtilis S. aureus cerevisiae nidulans B. napus thaliana N. tabacum esculentum P. hybrida Z. mays entoercolitica S. typhi E. coli Ą. Ą. ഗ

gure Ēų

| | 151 | | | | 200 |
|-------------------|-------------|-------------|------------|---|---|
| PG2982 | DMKT | SFIGDASLSK | RPMGRVLNPL | REMGVQVEAA | DGDRMPLT |
| LBAA | DMKT | SFIGDASLSK | RPMGRVLNPL | REMGVQVEAA | DGDRMPLT |
| Agrobacterium CP4 | • | TFIGDASLTK | RPMGRVLNPL | REMGVQVKSE | DGDRLPVT |
| B. subtilis | PFYS | AVAGDESIAK | RPMKRVTEPL | KKMGAKIDGR | AGGEFTPL |
| S. aureus | GNES | VLSGDVSIGK | RPMDRVLRPL | KLMDANIEG. | IEDNYTPL |
| | NST. SSQKYI | VLTGNARMQQ | RPIAPLVDSL | RANGTKIEYL | NNEGSLPIKV |
| ⋖ | NSSTVDSS | VLTGNNRMKQ | RPIGDLVDAL | TANVLPLNTS | KGRASLPLKI |
| B. napus | GGNASY | VLDGVPRMRE | RPIGDLVVGL | KQLGADVECT | LGINCPPVRV |
| A. thaliana | GGNASY | VLDGVPRMRE | RPIGDLVVGL | KQLGADVECT | LGTNCPPVRV |
| N. tabacum | GGHSRY | VLDGVPRMRE | RPIGDLVDGL | KQLGAEVDCF | LGTNCPPVRI |
| L. esculentum | GGHSRY | VLDGVPRMRE | RPIGDLVDGL | KQLGAEVDCS | LGTNCPPVRI |
| P. hybrida | GGNSRY | VLDGVPRMRE | RPISDLVDGL | KQLGAEVDCF | LGTKCPPVRI |
| Z. mays | GGNATY | VLDGVPRMRE | RPIGDLVVGL | KQLGADVDCF | LGTDCPPVRV |
| S. dallinarum | GQNEI | VLTGEPRMKE | RPIGHLVDSL | RQGGANIDYL | EQENYPPLRL |
| L. | GONEI | VLTGEPRMKE | RPIGHLVDSL | RQGGANIDYL | EQENYPPLRL |
| S. typhi | GONEI | VLTGEPRMKE | RPIGHLVDSL | RQGGANIDYL | EQENYPPLRL |
| E. coli | GSNDI | VLTGEPRMKE | RPIGHLVDAL | RLGGAKITYL | EQENYPPLRL |
| K, pneumoniae | GSNDI | VLTGEPRMKE | RPIGHLVDAL | RQGGAQIDYL | EQENYPPLRL |
| Y. entoercolitica | GKNDI | VLTGEPRMKE | RPIGHLVDAL | RQGGAQIDYL | EQENYRR.CI |
| H. influenzae | G.NHEV. EI | ILTGEPRMKE | RPILHLVDAL | RQAGADIRYL | ENEGYPPLAI |
| P. multocida | TPNREGKNEI | VLTGEPRMKE | RPIQHLVDAL | CQAGAEIQYL | EQEGYPPIAI |
| A. salmonicida | GSGEY | MLGGEPRMEE | RPIGHLVDCL | ALKGAHIQYL | KKDGYPPLVV |
| B. pertussis | GGDY | RLSGVPRMHE | RPIGDLVDAL | RQFGAGIEYL | GQAGYPPLRI |
| Consensus | | | RPL | 1 | t t 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 |

| 250 | TPGVTT | TPGVTT | TPGITT | AEGTTT | SKEPTI | .EPVTLALVG | . EPVTLRLVG | .LGDVEIEII | .LGDVEIEIV | .LGDVEIEII | .LGDVEIEII | .LGDVEIEII | .LGDVEIEII | . PKDTIIRVK | . PKDTIIRVK | . PEDTIIRVK | . PEDTVIRIK | . PODTVIAIK | EQDTEIQIQ. | . ENDTEIEII | .EADTEIEII | . PVIPRIHIK | SGODITIEW | 1 |
|-----|------------|------------|-------------------|-------------|------------|---------------|-------------|------------|-------------|------------|---------------|------------|------------|---------------|-------------|-------------|-------------|---------------|-------------------|---------------|--------------|----------------|------------|---|
| | LLAGLN | LLAGLN | LLAGLN | LLAGLQ | LFASLF | LMCAPYAE | LMCAPYAK | LMAAP.LA | LMSAP.LA | LMAAP.LA | LMAAP.LA | LMAAP.LA | LMAAP.LP | LMTAP.LA | LMTAP.LA | LMTAP.LA | LMTAP.LA | LMASP.LA | LMTAP.LA | LMSAP.LA | LMAAP.MA | LMAAPAMA | LMAAPVLARR | I |
| | MASAQVKSAV | MASAQVKSAV | MASAQVKSAV | VASAQIKSAV | VASAOVKSAI | TVSSQYVSSI | KVSSQYVSSL | SISSQYLTAL | SISSOYLTAL | SISSQYLTAL | SISSQYLTAL | SISSOYLTAL | SISSQYLSAL | SVSSOFLTAL | SVSSQFLTAL | SVSSQFLTAL | SVSSQFLTAL | SVSSQFLTAL | SVSSQFLTAL | SISSQFLTAL | SVSSQFLTAL | SVSSQFLTAF | SVSSQFLTAL | S-O |
| | TANPITYRVP | TANPITYRVP | TPTPITYRVP | SLKGIDYVSP | VIKGINYQME | GRIELAA | GNINLAA | GKVKLSG | GKVKLSG | GKVKLSG | GKVKLSG | GKVKLSG | GKVKLSG | GDIEVDG | GDIEVDG | GDIEVDG | GNVDVDG | GDVEVDG | GKLTVDG | GKVKIDG | GRIQIDG | GDVHVDG | GPVRVEG | 1 |
| 201 | LIGPK | LIGPK | IRGPK | SVSGA | IIKPS | YTDSVFKG | AASGGFAG | NANGGLPG | NANGGLPG | VSKGGLPG | VSKGGLPG | VSKGGLPG | NGIGGLPG | RGGFIG | RGGFTG | RGGFIG. | QGGFTG | RGGFTG | AGGFRG | RNK.GIKG | RNT.GLKG | DAK.GLWG | GGGSIRVD | |
| | PG2982 | LBAA | Agrobacterium CP4 | B. subtilis | S. aureus | S. cerevisiae | ⋖ | B. napus | A. thaliana | N. tabacum | L. esculentum | P. hybrida | Z. mays | S. qallinarum | Ţ | | E. coli | K. pneumoniae | Y. entoercolitica | H. influenzae | P. multocida | A. salmonicida | ф | Consensus |

Figure 20E

KYKSPGKAYV KLVGQ.TIDV KLTGO.VIDV KLTAA.DIFV RYIKPADFHV HYINPSEYVI RYVNPAEYVI KYKSPGNAYV KYKSPGNAYV KYKSPGKAFV KYKSPGKAFV KYKSPKNAYV OYHSPGRYLV QYHSPGRYLV QYHSPGRYLV SYÓSPGTYLV QYQSPGDYLV **LYRSPGIYLV** SYISPNKYLV KLVGQ VRHIRITGQG EPYTYYIPKG **EEHTYHI PQG** WDRFFVKGGQ VRTIRLEGRG WDRFFVKGGQ WDKFLVRGGQ WDRFFVRGGQ .. INTTPEAI WDRFLVKGGQ WDRFYIKGGQ YQQFVVKGGQ YQQFVVKGGQ YQQFVVKGGQ YORFIVRGNO YQIFHIKGGQ YOKFQVKGNQ YORFLVKGHQ YKLFYIKGNQ YQQFVVKGGQ IN. VET. STT DLTVETDKDG DLTVETDKDG NLTVETDADG ID. VQKSTT .. AEHSDS ..VEHSDS .VEHTSS ..VEHSSG .VEHSSS AEHSDS IAN. HH IAN. HH IAN. HH IEN.QH VEN. QA VVH. EN V. RRDG KLSEDQTS.. PIEAEGLS.. VE. ĞΕ. TEKMLQGFGA MTLKLMERFG TEKMLOGFGA TEKMLQGFGA TERMLSAFGV MTIKMMEKFG MTLKLMERFG MTLKLMERFG MTLKLMERFG MTLRLMERFG ITLHLMKTFG ITLHLMKAFG ITLAMMRDFG ITLHIMNSSG MTTAMMRSFG MTLKLMERFG ITLNLMKTFG ITLNLMKTFG ITLNLMKTFG ITLNLMKTFG ITLKMMOTFG TETMFKHFNI GKPISKLYVD VIEPVMTRDH VTEPHKSRDH GKPISQPYID VIEPVMTRDH VIEPIMTRDH DKLISVPYVE DKLISVPYVE DKLISVPYVE IKELDVSRNH DKLISVPYVE DKLISVPYVE DKLISIPYVE GELVSKPYID GELVSKPYID GELVSKPYID GELVSKPYID GELVSKPYID GELVSKPYID GELVSKPYID GDLVSKPYID GELVSRPYID subtilis cerevisiae PG2982 Agrobacterium CP4 S. aureus nidulans B. napus thaliana N. tabacum esculentum P. hybrida Z. mays gallinarum typhimurium pneumoniae entoercolitica H. influenzae P. multocida salmonicida pertussis Consensus E. coli s. typhi ⋖ S \succ

May 27, 1997

qure

| 350 T. T. T. T. T. MM. PTRAGI. | PTRTGLI | DVTILNVLMN PTRTGLI LTLQEMGADI | RIVLKNVGLN PTRTGII DVLQNMGAKL | DVTIHNVGIN OTRSGII DIVEKMGGNI | TVTVPNIGFE SLQGDARFAR DVLKPMGCKI | TCTVPNIGSA SLQGDARFAV EVLRPMGCTV | TVTVEGCGTT SLQGDVKFA. EVLEKMGCKV | TVTVEGCGTT SLQGDVKFA. EVLEKMGCKV | TVTVEGCGTS SLQGDVKFA. EVLEKMGAEV | TVTVEGCGTS SLOGDVKFA. EVLEKMGAEV | TITVEGCGTN SLQGDVKFA. EVLEKMGAEV | TVTVEGCGTT SLQGDVKFA. EVLEMMGAKV | TVKVTGIGRK SMQGDIRFA. DVLEKMGATI | TVKVTGIGRK SMQGDIRFA. DVLEKMGATI | TVKVTGIGGK SMQGDIRFA. DVLHKMGATI | TVKVTGIGRN SMQGDIRFA. DVLEKMGATI | TVKVTGIGRN SVQGDIRFA. DVLEKMGATV | TVRVTGIGKO SVQGDTKFA. DVLEKMGAKI | KVKVTGIGKN SIQGDRLFA. DVLEKMGAKI | KVKVTGVGKN SIQGDRLFA. DVLEKMGAHI | | KVRVTGIGKH SI.GDIHFA. DVLERMGARI | SI.GDIHFA. SIQGDVAFA. | SI.GDIHFA. SIQGDVAFA. |
|--|--------------|-------------------------------|-------------------------------|-------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------|----------------------------------|--------------------------|--------------------------|
| FGDESSTAFF LVAALLVEGS DVT: PGDPSSTAFP LVAALLVPGS DVT: | T,VAAL,LVPGS | | PGDISSAAFF LAAGAMVPNS RIVI | PGDISSAAFF IVAALITPGS DVT] | ESDASSATYP LAFAA.MTGT TVTV | LAVAA.VTGT | EGDASSASYF LAGAA.ITGE TVTV | EGDASSASYF LAGAA.ITGE TVTV | EGDASSASYF LAGAA.VTGG TVTV | EGDASSASYF LAGAA.VTGG TVTV | EGDASSASYF LAGAA.VTGG TITV | EGDASSASYF LAGAA.ITGG TVTV | EGDASSASYF LAAGA.IKGG TVKN | EGDASSASYF LAAGA.IKGG TVKV | EGDASSASYF LAAGG.IKGG TVKV | EGDASSASYF LAAAA.IKGG TVKV | EGDASSASYF LAAGA.IKGG TVKV | EGDASSASYF LAAAA.IKGG TVRV | EGDASSASYF LAAGA.IK.G KVKV | EGDASSASYF LAAAA.IK.G KVKV | EGDASSASYF LAAGA.IK.G KVRV | EGDASTASYE LALGA IGGG PVRV | | |
| | LBAA LBAA | | | | | • | | | | ulentum | P. hybrida | | • | • • | S. typhi | • • | | ercolitica | | P. multocida E | A. salmonicida E | | Ī | percussis |

Figure 20G

5,633,435

| | 351 | | | | 400 |
|--------|-------------|-------------|-----------------|-------------------|------------|
| ΕVΙ | EVLNARLAGG | EDVADLRVR. | ASKLKGVVVP | PERAPSMIDE | YPVLAIAASF |
| EVL | EVLNARLAGG | EDVADLRVR. | ASKLKGVVVP | PERAPSMIDE | YPVLAIAASF |
| EVI | EVINPRLAGG | EDVADLRVR. | SSTLKGVTVP | EDRAPSMIDE | YPILAVAAAF |
| EIK | EIKPSADSGA | EPYGDLIIE. | TSSLKAVEIG | GDIIPRLIDE | IPIIALLATQ |
| OI. | OL. FNOTTGA | EPTASIRIQY | TPMLQPITIE | GELVPKAIDE | LPVIALLCTQ |
| , : | .TOTATS | TTVSGPPV | GTLKPLK | HVDMEPMTDA | FLTACVVAAI |
| • | EQTETS | TTVTGPSD | GILRATS | KRGYGT.NDR | CVPRCFRTGS |
| • | SWTENS. | VTVTGPSRDA | FGMRHLRAV. | DVNMNKMPDV | AMTLAVVALF |
| • | SWTENS. | VTVTGPPRDA | FGMRHLRAI. | DVNMNKMPDV | AMTLAVVALF |
| • | TWTENS. | VTVKGPPRNS | SGMKHLRAV. | DVNMNKMPDV | AMTLAVVALF |
| • | TWTENS. | VTVKGPPRNS | SGMKHLRAI. | DVNMNKMPDV | AMTLAVVALF |
| • | .TWTENS | VTVKGPPRSS | SGRKHLRAI. | DVNMNKMPDV | AMTLAVVALY |
| • | .TWTETS | VTVTGPPREP | FGRKHLKAI. | DVNMNKMPDV | AMTLAVVALF |
| : | . TWGDDF | IA | CTRGELHAI. | DMDMNHI PDA | AMTIATTALF |
| • | .TWGDDF | IA | CTRGELHAI. | DMDMNHIPDA | AMTIATTALF |
| : | .TWGDDF | IA | CTRGELHAI. | DMDMNHI PDA | AMTIATTALF |
| • | . CWGDDY | IS | CTRGELNAI. | DMDMNHI PDA | AMTIATAALF |
| • | .TWGEDY | IA | CTRGELNAI. | DMDMNHIPDA | AMTIATAALF |
| • | . SWGDDY | I | CSRGELQGI. | DMDMNHIPDA | AMTIATTALF |
| : | . TWGEDF | J | AEHAELNGI. | DMDMNHIPDA | AMTIATTALF |
| • | .TWGDDF | I | VEKGNLKGI. | DMDMNHIPDA | AMTIATTALF |
| • | . TWGDDF | I | AEQGPLHGV. | DMDMNHI PDV | GHDHSGOSHC |
| : | . RYGPGW | IETRGVRVAE | GGRLKAF. | DADFNLIPDA | AMTAATLALY |
| i I | 1 1 1 | 1 1 1 1 1 1 | 1 1 1 1 1 1 1 1 | - Q | i.i. |

| | 401 | | | | 450 |
|-------------------|-------------------------|------------|-------------|--------------------------------------|-------------|
| .PG2982 | AEG | ETVMDGLDEL | RVKESDRLAA | VARGLEANGV | DCTEGEMSLT |
| LBAA | AEG | ETVMDGLDEL | RVKESDRLAA | VARGLEANGV | DCTEGEMSLT |
| Agrobacterium CP4 | AEG | ATVMNGLEEL | RVKESDRLSA | VANGLKLNGV | DCDEGETSIV |
| B. subtilis | AEG | TTVIKDAAEL | KVKETNRIDT | VVSELRKLGA | EIEPTADGMK |
| | AVG | TSTIKDAEEL | KVKETNRIDT | TADMLNLLGF | ELQPTNDGLI |
| ה | SHDSDPNSAN | TTTIEGIANO | RVKECNRILA | MATELAKFGV | KTTELPDGIQ |
| . ⋖ | HRPMEKSQTT | PPVSSGIANQ | RVKECNRIKA | MKDELAKFGV | ICREHDDGLE |
| | ADG | PTTIRDVASW | RVKETERMIA | ICTELRKLGA | TV. EEGSDYC |
| | ADG | PTTIRDVASW | RVKETERMIA | ICTELRKLGA | TV. EEGSDYC |
| • | ADG | PTAIRDVASW | RVKETERMIA | ICTELRKLGA | TV.VEGSDYC |
| υ | ADG | PTTIRDVASW | RVKETERMIA | ICTELRKLGA | TV.VEGSDYC |
| | ADG | PTAIRDVASW | RVKETERMIA | ICTELRKLGA | TV. EEGPDYC |
| Z. mavs | ADG | PTAIRDVASW | RVKETERMVA | IRTELTKLGA | SV. EEGPDYC |
| S. dallinarum | AKG | TTTLRNIYNW | RVKETDRLFA | MATELRKVGA | EV. EEGHDYI |
| ىد | | TTTLRNIYNW | RVKETDRLFA | MATELRKVGA | EV. EEGHDYI |
| | AKG | TTTLRNIYNW | RVKETDRLFA | MATELRKVGA | EV. EEGHDYI |
| E. Coli | | TTRLRNIYNW | RVKETDRLFA | MATELRKVGA | EV. EEGHDYI |
| K. pneumoniae | ARG | TTTLRNIYNW | RVKETDRLFA | MATELRKVGA | EV. EEGEDYI |
| Y. entoercolitica | ADG | PTVIRNIYNW | RVKETDRLSA | MATELRKVGA | EV. EEGQDYI |
| | SNG | ETVIRNIYNW | RVKETDRLTA | MATELRKVGA | EV. EEGEDFI |
| | | ETVIRNIYNW | RVKETDRLTA | MATELRKVGA | EV. EEGEDFI |
| A. salmonicida | | VPPHSQHLQL | AVRD. DRCTP | CTHGHRRAQA | GVSEEGTTFI |
| | ADG | PCRLRNIGSW | RVKETDRIHA | MHTELEKLGA | GV.QSGADWL |
| | 1 1 1 1 1 1 1 1 1 1 1 1 | | -VR | 1 1 1 1 1 1 1 1 | |

| 500 | 4 | 8 | T | S: | VNSQNERDEV | VTPQ | A | A | A | A | A | A | | S | 8 | S | S | S | S | S | 8. | | f f l l |
|-----|--------------------------|-------------------|-------------|--------------|-----------------------|------------------|----------------|----------------|----------------|----------------|----------------|----------------|---------------|----------------|--------------|----------------|---------------|-------------------|----------------|----------------|----------------|----------------|---|
| | AMSFLVMGLA AMSFLVMGLA | AMSFLVMGLV | GMMLGIASCI | GMMLAVACVL | AMSFSLLAGM | AFSFSVL.SL | AMAFSLAAC. | AMAFSLAAC. | AMAFSLAAC. | AMAFSLAAC. | AMAFSLAAC. | AMAFSLAAC. | AMCFSLVAL. | AMCFSLVAL. | AMCFSLVAL. | AMCFSLVAL. | AMCFSLVAL. | AMCFSLVAL. | AMCFSLIAL. | AMCFALIAL. | AMCFSLVAL. | AMCFLLAAF. | 1 |
| | TVATHLDHRI TVATHLDHRI | AVATHLDHRI | AVSSHGDHRI | DILTDHRI | GVCTYDDHRV | GVFCYDDHRV | EIDTYDDHRM | EIDTYDDHRM | EIDTYDDHRM | EIDTYDDHRM | DIDTYDDHRM | AIDTYDDHRM | DIGTYNDHRM | DIGTYNDHRM | DIGTYNDHRM | EIATYNDHRM | EIGTYNDHRM | EIGTYNDHRM | NIETYNDHRM | ELNI.HDHRM | R. HLQRSRI | HIGTWDDHRM | R- |
| | VRGRPDGKGL GGG | S | VYGKQTLKGGA | IHPSEFKTN AT | VHGLNSIKDL KVPSDSSGPV | IDGIDR.SNL RQPVG | VITP. PAKV KPA | VITP. PKKV KTA | IITP. PEKL NVT | IITP. PEKL NVT | IITP. PEKL NVT | IITP. PEKL NVT | RITPPAKL QHA | RITP. PAKL QHA | RITPPAKL QHA | RITP. PEKL NFA | RITPPLTL QFA | RVVPPAQL IAA | RIQPLALNQF KHA | RIQPLNLAQF QHA | TRDAADPAQA RRD | EVAPPEPGGW RDA | |
| | PG2982 | Agrobacterium CP4 | B. subtilis | S. aureus | S. cerevisiae | A. nidulans | B. napus | A. thaliana | N. tabacum | L. esculentum | P. hybrida | Z. mays | S. gallinarum | ப | | E. coli | K. pneumoniae | Y. entoercolitica | H. influenzae | P. multocida | A. salmonicida | B. pertussis | Consensus |

ELSIL.. EQLARLSQIA EHLNKLSKKS EQLARMSTPA EQLARMSTPA EQLARMSTPA EQLARISQAA GOLARISTLA DLMAGLGAKI DVLQQYSKH. DMMPGLGAKI DMMPGLGAKI DVLQQYSKH. DVLSTFVKN. DVLH.... QVLERITKH EVLOKYSKH OVLESITKH MIATSFPEFM MIATSFPEFM MIATSFPEFM CTGKTWPGWW CVGKTWPGWW CTRKTFPDYF CTRKTFPDYF CTRKTFPNYF CTRKTFPDYF CTRKTFPNYF CTAKTFPDYF CTAKTFPDYF AIHVSYPTFF CTRKTFPDYF CTAKTFPDYF CTAKTFPDYF CTAKTFPDYF CTAKTFPDYF CVSKTFPDYF SEPVKIKOFD DVPITINDSG EKPVTVDDSN EKPVTVDDSN ENPVTVDDAT EEPIEIEHTD .. PTLILEKE DVPVTIKDPG DVPVTIKDPG DVPVTIKNPG ANPVRILERH DVPVTINDPG EVPVTIRDPG DTPVTILDPK DTPVTILDPK DTPVTILDPK DTPVTILDPK **JTPVTILDPK** DTPVTILDPK NTPVTILDPK KTSVTILDPS PAAVRILDPG S. aureus Agrobacterium CP4 B. subtilis cerevisiae nidulans B. napus thaliana N. tabacum esculentum P. hybrida Z. mays typhimurium coli K. pneumoniae entoercolitica H. influenzae P. multocida salmonicida gallinarum pertussis Consensus ທ

| U.S. | Patent |
|------|---------------|
|------|---------------|

| May | 27, | 1997 |
|-----|-----|------|
|-----|-----|------|

| Sheet | 55 | of | 70 |
|-------|--------|----|----|
| | \sim | O. | ,, |

| t | May 27, 1997 | Sheet 55 of 70 | 5,633,435 |
|---|--------------|----------------|-----------|
| | | | |

| 09 | 120 | 180 | 240 | 292 | 340 | 388 | 436 | 484 | | |
|---|---|---|--|---|--|--|--|--|------------|--|
| ACGGGCTGTA ACGGTAGTAG GGGTCCCGAG CACAAAAGCG GTGCCGGCAA GCAGAACTAA | TITCCATGGG GAATAATGGT ATTTCATTGG TTTGGCCTCT GGTCTGGCAA TGGTTGCTAG | GCGATCGCCT GTTGAAATTA ACAAACTGTC GCCCTTCCAC TGACCATGGT AACGATGTTT | TITACTICCI IGACTAACCG AGGAAAATIT GGCGGGGGC AGAAAIGCCA ATACAATITA | GCTTGGTCTT CCCTGCCCCT AATTTGTCCC CTCC ATG GCC TTG CTT TCC CTC Met Ala Leu Leu Ser Leu 1 | AAC AAT CAT CAA TCC CAT CAA CGC TTA ACT GTT AAT CCC CCT GCC CAA Asn Asn His Gln Ser His Gln Arg Leu Thr Val Asn Pro Pro Ala Gln 10 | GGG GTC GCT TTG ACT GGC CGC CTA AGG GTG CCG GGG GAT AAA TCC ATT Gly Val Ala Leu Thr Gly Arg Leu Arg Val Pro Gly Asp Lys Ser Ile 25 | TCC CAT CGG GCC TTG ATG TTG GGG GCG ATC GCC ACC GGG GAA ACC ATT Ser His Arg Ala Leu Met Leu Gly Ala Ile Ala Thr Gly Glu Thr Ile 40 | ATC GAA GGG CTA CTG TTG GGG GAA GAT CCC CGT AGT ACG GCC CAT TGC Ile Glu Gly Leu Leu Gly Glu Asp Pro Arg Ser Thr Ala His Cys 55 65 70 | Figure 21A | |

| U.S. Pate | ent | May 27, 1 | 1997 | Sheet 56 o | of 70 | 5,63 | 3,435 |
|--|--|---|---|---|---|---|------------|
| | | | | | | | |
| 532 | 580 | 628 | 676 | 724 | 772 | 820 | |
| GAA ATC AGC GAA CTA AAT TCA GAA AAA ATC Glu ile Ser Glu Leu Asn Ser Glu Lys ile 80 | CTG GGA CAG TTG CAG GAA CCC AGT ACC GTT Leu Gly Gln Leu Gln Glu Pro Ser Thr Val 95 | GGC ACC ATG CGC TTA ATG TTG GGC TTG Gly Thr Thr Met Arg Leu Met Leu Gly Leu 110 | TGT TTA TTC ACC GTC ACC GGC GAT GAT TCC Cys Leu Phe Thr Val Thr Gly Asp Asp Ser 125 | TCC CGG GTA ATT CAA CCC TTG CAA CAA ATG Ser Arg Val Ile Gln Pro Leu Gln Gln Met 145 | CGG AGT AAC GGC AAG TTT GCG CCG CTG GCA Arg Ser Asn Gly Lys Phe Ala Pro Leu Ala 160 | AAA CCG ATC CAT TAC CAT TCC CCC ATT GCT Lys Pro Ile His Tyr His Ser Pro Ile Ala 175 | Figure 21B |
| GGA GCA GIY Ala 75 | CGG GGT Arg Gly | AAC TCT Asn Ser | AAA GAT Lys Asp | CCC ATG Pro Met 140 | TGG GCC Trp Ala | CAA TTA Gln Leu | |
| GCC ATG G Ala Met G | CAG GGT C Gln Gly P | GCG GGG A Ala Gly A 105 | GGG CAA A Gly Gln I | CAC CGC C His Arg F | AAA ATT T Lys Ile 1 | GGT AGC CGly Ser G | |
| TTT CGG G Phe Arg A | ATC GTT C Ile Val G | TTG GAT G Leu Asp A | CTA GCC G Leu Ala G 120 | CTC CGT C. Leu Arg H 135 | GGG GCA A Gly Ala L | GTC CAG G Val Gln G | |

| U.S. | Patent |
|------|--------|
| | |

| Sheet | 57 | Ωf | 70 |
|-------|-----------|-----|------------|
| DHEEL | JI | OI. | <i>1</i> U |

| 5. | 633 | ,435 |
|-----|-----|------|
| ~ 7 | ~~ | , |

| 898 | 916 | 964 | 1012 | 1060 | 1108 | 1156 |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| GAG Glu | GAA Glu | ACC Thr 230 | GTG Val | GCA Ala | AAC Asn | GAC Asp |
| ACC Thr | AGC Ser | GTA Val | CGG Arg 245 | GCG Ala | ATT Ile | GCG Ala |
| ACC Thr | CAT His | CCA Pro | CAA | GTG Val 260 | GGC G1y | 666 G1y |
| TTA Leu 195 | GAT Asp | GAT Asp | 666 G1y | TTA | GTA Val 275 | ATG Met |
| 666 61y | CGG Arg 210 | ATT Ile | ACG Thr | TGG Trd | AAT Asn | CAG Gln 290 |
| GCG Ala | TCC | ACC Thr 225 | TTA Leu | TTT Phe | GAA Glu | GCC Ala |
| CTA | CTA Leu | TTA | CAT His 240 | GCC Ala | GTG Val | TTG |
| TTG Leu | GCT Ala | AAA Lys | GCC Ala | GCG Ala 255 | TTG Leu | GTG Val |
| CTG Leu 190 | CCA Pro | GCC Ala | CCG Pro | TCG Ser | TTG Leu 270 | GAA Glu |
| TGC Cys | GAA Glu 205 | GGA Gly | 66C 61y | AGC Ser | GAA Glu | TTG Leu 285 |
| TCC | ACA Thr | TTT Phe 220 | CAT His | ATC Ile | TCA Ser | GTG Val |
| AAG Lys | GTT Val | GCC Ala | GTC Val 235 | GAC Asp | GGA Gly | 666 G1y |
| GTA Val | ACG Thr | CAG Gln | ACT Thr | GGG Gly 250 | CCT | ACA Thr |
| CAG Gln 185 | ACC Thr | TTG Leu | GTC Val | CCA Pro | TTG Leu 265 | AGG Arg |
| GCC Ala | GAC Asp 200 | ATG Met | AGC | GTG Val | ATT Ile | ACC Thr |
| TCA Ser | $_{\rm GGG}$ | CGC Arg 215 | CAT His | GTG Val | TCC | CCC |
| | | | | | | |

| U.S | . Pate | ent | May 27, | 19 97 | Sheet 58 c | of 70 | 5,63 | 33,435 |
|---|---|---|---|---|---|---|---|------------|
| | | | | | | | | |
| 1001 | 1 | 1252 | 1300 | 1348 | 1396 | 1444 | 1492 | |
| מיני מיני מיני מיני מיני מיני מיני מיני | c CCG GAG AAT GAA CGA TIG GIA ACG GGA CCG GIA GCA GAI r Pro Glu Asn Glu Arg Leu Val Thr Gly Glu Pro Val Ala Asp 300 | G GTT AGG GCA AGC CAT CTC CAG GGT TGC ACC TTC GGC GGC GAA g Val Arg Ala Ser His Leu Gln Gly Cys Thr Phe Gly Gly Glu 325 | T CCC CGA CTG ATT GAT GAA ATT CCC ATT TTG GCA GTG GCG GCG e Pro Arg Leu Ile Asp Glu Ile Pro Ile Leu Ala Val Ala Ala 330 | T GCA GAG GGC ACT ACC CGC ATT GAA GAT GCC GCA GAA CTG AGG e Ala Glu Gly Thr Thr Arg Ile Glu Asp Ala Ala Glu Leu Arg 345 | A GAA AGC GAT CGC CTG GCG GCC ATT GCT TCG GAG TTG GGC AAA s Glu Ser Asp Arg Leu Ala Ala Ile Ala Ser Glu Leu Gly Lys 0 | G GCC AAA GTC ACC GAA TTT GAT GAT GGC CTG GAA ATT CAA GGG y Ala Lys Val Thr Glu Phe Asp Asp Gly Leu Glu Ile Gln Gly 380 | C CCG TTA CAA GGG GCC GAG GTG GAT AGC TTG ACG GAT CAT CGC r Pro Leu Gln Gly Ala Glu Val Asp Ser Leu Thr Asp His Arg 395 | Figure 21D |
| ì | ACC | CGG | ATT | TTT | AAA Lys 360 | GGG G1y | AGC | |

GTT Val

ATG Met 375

GGA GIY

GCC TTT GCA GAG GGC ACT ACC Ala Phe Ala Glu Gly Thr Thr 345

ATT Ile

CTG

ATT Ile 295

| U.S. Patent | May : | ıy 27, 1997 | | eet 59 (| of 70 | | 5, | 633,435 |
|---|---|---|---|---|---|---|----------------------|------------|
| 1540 | 1588 | 1635 | 1695 | 1755 | 1815 | 1875 | 1894 | |
| ATT GCC ATG GCG TTG GCG ATC GCC GCT TTA GGT AGT GGG GGG CAA ACA Ile Ala Met Ala Leu Ala Ile Ala Ala Leu Gly Ser Gly Gly Gln Thr 410 | ATT ATT AAC CGG GCG GAA GCG GCC GCC ATT TCC TAT CCA GAA TTT TTT Ile Ile Asn Arg Ala Glu Ala Ala Ala Ile Ser Tyr Pro Glu Phe Phe 435 | GGC ACG CTA GGG CAA GTT GCC CAA GGA TAAAGTTAGA AAAACTCCTG Gly Thr Leu Gly Gln Val Ala Gln Gly 440 | GGCGGTTTGT AAATGTTTTA CCAAGGTAGT TTGGGGTAAA GGCCCCAGCA AGTGCTGCCA | GGGTAATTTA TCCGCAATTG ACCAATCGGC ATGGACCGTA TCGTTCAAAC TGGGTAATTC | TCCCTTTAAT TCCTTAAAAG CTCGCTTAAA ACTGCCCAAC GTATCTCCGT AATGGCGAGT | GAGTAGAAGT AATGGGGCCA AACGGCGATC GCCACGGGAA ATTAAAGCCT GCATCACTGA | CCACTTATAA CTTTCGGGA | Figure 21E |

| .S. | Patent | May 2 | y 27, 1997 Sheet 6 | | of 70 | 5,63 | 3,435 |
|--|--|---|--|--|--|--|------------|
| 09 | 115 | 163 | 211 | 259 | 307 | 355 | |
| TITAAAAACA ATGAGITAAA AAATTAITIT TCTGGCACAC GCGCITITITI TGCATTITIT | CTCCCATTTT TCCGGCACAA TAACGTTGGT TTTATAAAAG GAAATG ATG ATG ACG Met Met Thr 1 | AAT ATA TGG CAC ACC GCG CCC GTC TCT GCG CTT TCC GGC GAA ATA ACG Asn lle Trp His Thr Ala Pro Val Ser Ala Leu Ser Gly Glu Ile Thr 5 | ATA TGC GGC GAT AAA TCA ATG TCG CAT CGC GCC TTA TTA TTA GCA GCG Ile Cys Gly Asp Lys Ser Met Ser His Arg Ala Leu Leu Leu Ala Ala 20 | TTA GCA GAA GGA CAA ACG GAA ATC CGC GGC TTT TTA GCG TGC GCG GAT Leu Ala Glu Gly Gln Thr Glu Ile Arg Gly Phe Leu Ala Cys Ala Asp 45 | TGT TTG GCG ACG CGA GCA TTG CGC GCA TTA GGC GTT GAT ATT CAA Cys Leu Ala Thr Arg Gln Ala Leu Arg Ala Leu Gly Val Asp Ile Gln 60 | AGA GAA AAA GAA ATA GTG ACG ATT CGC GGT GTG GGA TTT CTG GGT TTG Arg Glu Lys Glu Ile Val Thr Ile Arg Gly Val Gly Phe Leu Gly Leu 75 | Figure 22A |

U.S. Patent

| U.S. Pate | ent | May 27, 1 | 1997 | Sheet 61 of 70 | | 5,633,435 | |
|--|---|---|---|---|---|---|------------|
| | | | | | | | |
| 403 | 451 | 499 | 547 | 595 | 643 | 691 | |
| CAG CCG CCG AAA GCA CCG TTA AAT ATG CAA AAC AGT GGC ACT AGC ATG Gln Pro Pro Lys Ala Pro Leu Asn Met Gln Asn Ser Gly Thr Ser Met 85 | CGT TTA TTG GCA GGA ATT TTG GCA GCG CAG CGC TTT GAG AGC GTG TTA Arg Leu Leu Ala Gly Ile Leu Ala Ala Gln Arg Phe Glu Ser Val Leu 100 | TGC GGC GAT GAA TCA TTA GAA AAA CGT CCG ATG CAG CGC ATT ATT ACG Cys Gly Asp Glu Ser Leu Glu Lys Arg Pro Met Gln Arg Ile Ile Thr 125 | CCG CTT GTG CAA ATG GGG GCA AAA ATT GTC AGT CAC AGC AAT TTT ACG Pro Leu Val Gln Met Gly Ala Lys Ile Val Ser His Ser Asn Phe Thr 135 | GCG CCG TTA CAT ATT TCA GGA CGC CCG CTG ACC GGC ATT GAT TAC GCG Ala Pro Leu His Ile Ser Gly Arg Pro Leu Thr Gly Ile Asp Tyr Ala 150 | TTA CCG CTT CCC AGC GCG CAA TTA AAA AGT TGC CTT ATT TTG GCA GGA Leu Pro Leu Pro Ser Ala Gln Leu Lys Ser Cys Leu Ile Leu Ala Gly 165 | TTA TTG GCT GAC GGT ACC ACG CGG CTG CAT ACT TGC GGC ATC AGT CGC Leu Leu Ala Asp.Gly Thr Thr Arg Leu His Thr Cys Gly Ile Ser Arg 180 | Figure 22B |

| U.S. Pate | S. Patent May 27, 1997 Sheet 62 of 70 | | of 70 | 5,63 | 33,435 | | |
|---|---|---|---|---|---|---|------------|
| 739 | 787 | 835 | 883 | 931 | 979 | 1027 | |
| GAC CAC ACG GAA CGC ATG TTG CCG CTT TTT GGT GGC GCA CTT GAG ATC Asp His Thr Glu Arg Met Leu Pro Leu Phe Gly Gly Ala Leu Glu Ile 205 | AAG AAA GAG CAA ATA ATC GTC ACC GGT GGA CAA AAA TTG CAC GGT TGC Lys Lys Glu Gln Ile Ile Val Thr Gly Gly Gln Lys Leu His Gly Cys 215 | GTG CTT GAT ATT GTC GGC GAT TTG TCG GCG GCG GCG TTT TTT ATG GTT Val Leu Asp Ile Val Gly Asp Leu Ser Ala Ala Ala Phe Phe Met Val 230 | GCG GCT TTG ATT GCG CCG CGC GCG GAA GTC GTT ATT CGT AAT GTC GGC Ala Ala Leu Ile Ala Pro Arg Ala Glu Val Val Ile Arg Asn Val Gly 245 | ATT AAT CCG ACG CGG GCA ATC ATT ACT TTG TTG CAA AAA ATG GGC Ile Asn Pro Thr Arg Ala Ala Ile Ile Thr Leu Leu Gln Lys Met Gly 260 | GGA CGG ATT GAA TTG CAT CAT CAG CGC TTT TGG GGC GCC GAA CCG GTG Gly Arg Ile Glu Leu His His Gln Arg Phe Trp Gly Ala Glu Pro Val 285 | GCA GAT ATT GTT TAT CAT TCA AAA TTG CGC GGC ATT ACG GTG GCG Ala Asp Ile Val Tyr His Ser Lys Leu Arg Gly Ile Thr Val Ala 300 | Figure 22C |

| U.S. Pat | ent | May 27, | 1997 | Sheet 63 | of 70 | 5,63 | 3,435 |
|---|---|---|---|---|---|---|------------|
| 1075 | 1123 | 1171 | 1219 | 1267 | 1315 | 1363 | |
| CCG GAA TGG ATT GCC AAC GCG ATT GAT GAA TTG CCG ATT TTT TTT ATT Pro Glu Trp Ile Ala Asn Ala Ile Asp Glu Leu Pro Ile Phe Phe Ile 310 | GCG GCA GCT TGC GCG GAA GGG ACG ACT TTT GTG GGC AAT TTG TCA GAA Ala Ala Ala Cys Ala Glu Gly Thr Thr Phe Val Gly Asn Leu Ser Glu 325 | TTG CGT GTG AAA GAA TCG GAT CGT TTA GCG GCG ATG GCG CAA AAT TTA Leu Arg Val Lys Glu Ser Asp Arg Leu Ala Ala Met Ala Gln Asn Leu 340 | CAA ACT TTG GGC GTG GCG TGC GAC GTT GGC GCC GAT TTT ATT CAT ATA Gln Thr Leu Gly Val Ala Cys Asp Val Gly Ala Asp Phe Ile His Ile 360 | TAT GGA AGA AGC GAT CGG CAA TTT TTA CCG GCG CGG GTG AAC AGT TTT Tyr Gly Arg Ser Asp Arg Gln Phe Leu Pro Ala Arg Val Asn Ser Phe 375 | GGC GAT CAT CGG ATT GCG ATG AGT TTG GCG GTG GCA GGT GTG CGC GCG Gly Asp His Arg Ile Ala Met Ser Leu Ala Val Ala Gly Val Arg Ala 390 | GCA GGT GAA TTA TTG ATT GAT GAC GGC GCG GTG GCG GCG GTT TCT ATG Ala Gly Glu Leu Leu Ile Asp Asp Gly Ala Val Ala Ala Val Ser Met 405 | Figure 22D |

| U.S. Patent | May 27, 1997 | Shee | t 64 of 70 |
|-------------|---|---|-----------------|
| | 1411 | 1465 | 1479 |
| | GCC GCC GCA ATT GGT ATG AAT GTA GGA GAA Ala Ala Ile Gly Met Asn Val Gly Glu 430 | CAC GAT TGATGGTCCT AGCGGTGTTG GAAAAGGCAC His Asp | Figure 22E |
| | TTT GCC Phe Ala 425 | TGT | |
| | TTT CGC GAT Phe Arg Asp | AAT Asn 440 | |
| | CGC Arg | GCG AAA 1 Ala Lys 1 | GCTT |
| | TTT Phe | GCG Ala | GGTGGCGCAA GCTT |
| | CAA Gln | GAT Asp | 9299 |
| | CCG Pro 420 | AAA Lys | GGT |

5,633,435

| | ← | | | 40 |
|---------------------------|------------|------------|------------|-------------------|
| PG2982 | | HSASPKPATA | RRSEALTGEI | RIPGDKSISH |
| LBAA | MS | HSASPKPATA | RRSEALTGEI | RIPGDKSISH |
| Agrobacterium CP4 | MS | HGASSRPATA | RKSSGLSGTV | RIPGDKSISH |
| Synechocystis sp. PCC6803 | MALLSLNNHQ | SHQRLTVNPP | AQGVALTGRL | RVPGDKSISH |
| B. subtilis | • | MKR | DKVQTLHGEI | HIPGDKSISH |
| D. nodosus | • | . MMTNIWHT | APVSALSGEI | TICGDKSMSH |
| S. aureus | • | MVNEQII | DISGPLKGEI | EVPGDKSMTH |
| Consensus | | | 9-T | -I- <u>GDKS</u> H |
| | 41 | ٠ | | 80 |
| PG2982 | RSFMFGGLAS | GETRITGLLE | GEDVINTGRA | MQAMGAKI.R |
| LBAA | RSFMFGGLAS | GETRITGLLE | GEDVINTGRA | MQAMGAKI.R |
| Agrobacterium CP4 | RSFMFGGLAS | GETRITGLLE | GEDVINTGKA | MQAMGARI.R |
| Synechocystis sp. PCC6803 | RALMLGAIAT | GETIIEGLLL | GEDPRSTAHC | FRAMGAEISE |
| B. subtilis | RSVMFGALAA | GTTTVKNFLP | GADCLSTIDC | FRKMGVHI.E |
| D. nodosus | RALLLAALAE | GQTEIRGFLA | CADCLATRQA | LRALGVDI.Q |
| S. aureus | RAIMLASLAE | GVSTIYKPLL | GEDCRRTMDI | FRHLGVEI.K |
| Consensus | RMFA- | GID | LQ | WG |
| | 81 | | | 120 |
| PG2982 | KEGDVWIING | VGNGCLLQPE | AALDFGNAGT | GARLTMGLVG |
| LBAA | KEGDVWIING | VGNGCLLQPE | AALDFGNAGT | GARLTMGLVG |
| Agrobacterium CP4 | KEGDTWIIDG | VGNGGLLAPE | APLDFGNAAT | GCRLTMGLVG |
| Synechocystis sp. PCC6803 | LNSEKIIVQG | RGLGQLQEPS | TVLDAGNSGT | TMRLMLGLLA |
| B. subtilis | QSSSDVVIHG | KGIDALKEPE | SLLDVGNSGT | TIRLMLGILA |
| D. nodosus | REKEIVTIRG | VGFLGLQPPK | APLNMQNSGT | SMRLLAGILA |
| S. aureus | EDDEKLVVTS | PGYQ.VNTPH | QVLYTGNSGT | TTRLLAGLLS |
| SISHARMOD | | -GB- | I T | RLG |

| | 121 | | | 160 | |
|---------------------------|--------------|------------|------------|------------|--|
| PG2982 | DMKTSFI | GDASLSKRPM | GRVLNPLREM | GVQVEAADGD | |
| LBAA | TY. DMKTSFI | GDASLSKRPM | GRVLNPLREM | GVQVEAADGD | |
| Agrobacterium CP4 | VY.DFDSTFI G | GDASLTKRPM | GRVLNPLREM | GVQVKSEDGD | |
| Synechocystis sp. PCC6803 | GOKDCLFTVT G | GDDSLRHRPM | SRVIQPLQQM | GAKIWARSNG | |
| | | GDESIAKRPM | KRVTEPLKKM | GAKIDGRAGG | |
| | AQR.FESVLC G | GDESLEKRPM | QRIITPLVQM | GAKIVSHSNF | |
| S. aureus | | GDVSIGKRPM | DRVLRPLKLM | DANIEGIEDN | |
| Consensus | | GD-SRPM | -RVPLM | I | |
| | 161 | | | 200 | |
| PG2982 | RMPLTLIGPK 1 | TANPITYRVP | MASAQVKSAV | LLAGLNTPGV | |
| LBAA | | TANPITYRVP | MASAQVKSAV | LLAGLNTPGV | |
| Agrobacterium CP4 | | TPTPITYRVP | MASAQVKSAV | LLAGLNTPGI | |
| Synechocystis sp. PCC6803 | | QLKPIHYHSP | IASAQVKSCL | LLAGLTTEGD | |
| | EFTPLSVSGA S | SLKGIDYVSP | VASAQIKSAV | LLAGLQAEGT | |
| D. nodosus | T.APLHISGR E | PLTGIDYALP | LPSAQLKSCL | ILAGLLADGT | |
| S. aureus | YTPLIIKPS V | VIKGINYQME | VASAQVKSAI | LFASLFSKEP | |
| Consensus | ! ! ! ! ! ! | X-I | SAO-KS | ~LA-L | |
| | 201 | | | 240 | |
| PG2982 | TTVIEPVMTR D | DHTEKMLQGF | GADLT | VETDKDGVRH | |
| LBAA | TTVIEPVMTR D | DHTEKMLQGF | GADLT | VETDKDGVRH | |
| Agrobacterium CP4 | TTVIEPIMTR D | DHTEKMLQGF | GANLT | VETDADGVRT | |
| Synechocystis sp. PCC6803 | TTVTEPALSR D | DHSERMLQAF | GAKLT | IDPVTHSV | |
| | TTVTEPHKSR I | DHTERMLSAF | GVKLS | EDQTSV | |
| D, nodosus | TRLHTCGISR D | DHTERMLPLF | GGALE | IKKEQI | |
| S. aureus | TIIKELDVSR N | NHTETMFKHF | NIPIEAEGLS | INTTPEAIRY | |
| מונטמטטמטט | | -H-E-MIF | | | |

| | 241 | 280 |
|---------------------------|--|-------|
| PG2982 | IRITGQGKLV GQTIDVPGDP SSTAFPLVAA LLVEGSDVTI | 'TI |
| LBAA | IRITGOGKLV GOTIDVPGDP SSTAFPLVAA LLVEGSDVTI | ŢŢ, |
| Agrobacterium CP4 | | ŢŢ, |
| Svnechocystis sp. PCC6803 | .TVHGPAHLT GORVVVPGDI SSAAFWLVAA SILPGSELLV | ΓV |
| | SIAGGQKLT AADIFVPGDI SSAAFFLAAG AMVPNSRIVL | VL |
| D. nodosus | IVTGGQKLH GCVLDIVGDL SAAAFFMVAA LIAPRAEVVI | Λī |
| S. aureus | IKPADFHVPGDI SSAAFFIVAA LITPGSDVTI | TT. |
| Consensus | AA | 1 1 1 |
| | 281 | 320 |
| PG2982 | RNVLMNPTRT GLILTLQEMG ADIEVLNARL AGGEDVADLR | LR |
| LBAA | RNVLMNPTRT GLILTLQEMG ADIEVLNARL AGGEDVADLR | LR |
| Agrobacterium CP4 | LNVLMNPTRT GLILTLQEMG ADIEVINPRL AGGEDVADLR | LR |
| Synechocystis sp. PCC6803 | ENVGINPTRT GVLEVLAQMG ADITPENERL VTGEPVADLR | LR |
| | KNVGLNPTRT GIIDVLQNMG AKLEIKPSAD SGAEPYGDLI | LI |
| D. nodosus | RNVGINPTRA AIITLLQKMG GRIELHHQRF WGAEPVADIV | ΛI |
| S. aureus | HNVGINQTRS GIIDIVEKMG GNIQLFNQT. TGAEPTASIR | IR |
| Consensus | -NV <u>N-TR</u> MGE | · 1 |
| | | 360 |
| PG2982 | VR. ASKLKGV VVPPERAPSM IDEYPVLAIA ASFAEGETVM | VIM. |
| LBAA | VR. ASKLKGV VVPPERAPSM IDEYPVLAIA ASFAEGETVM | VM |
| Agrobacterium CP4 | VR. SSTLKGV TVPEDRAPSM IDEYPILAVA AAFAEGATVM | VM |
| Synechocystis sp. PCC6803 | VR.ASHLQGC TFGGEIIPRL IDEIPILAVA AAFAEGTTRI | ŔĬ |
| | IE.TSSLKAV EIGGDIIPRL IDEIPIIALL ATQAEGTTVI | ΛI |
| D. nodosus | VY.HSKLRGI TVAPEWIANA IDELPIFFIA AACAEGTTFV | ΈV |
| S. aureus | IQYTPMLQPI TIEGELVPKA IDELPVIALL CTQAVGTSTI | TI |
| מונים מסימסט | B-8B 11 | 1 |

Figure 23C

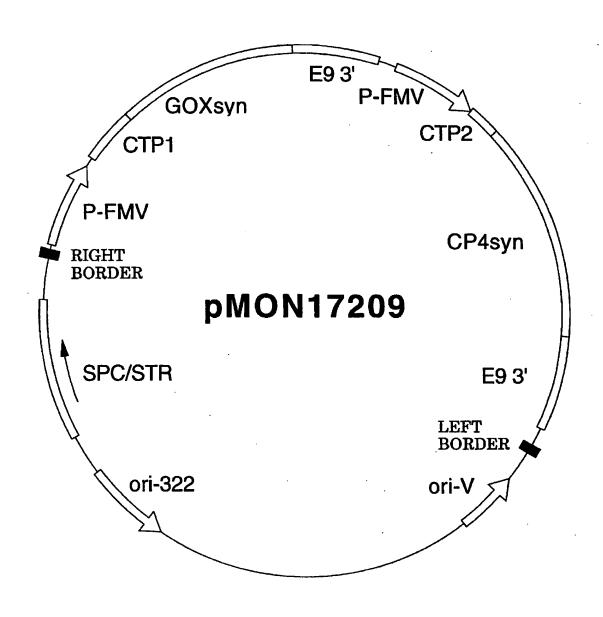


Figure 24

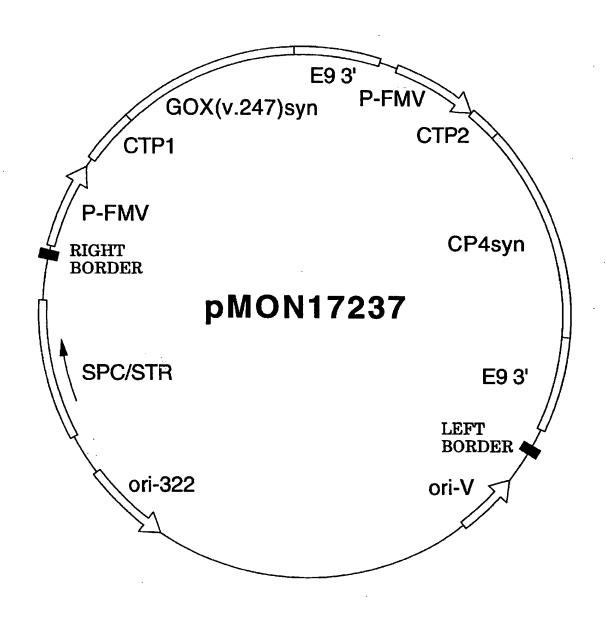


Figure 25